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Review

Needle-free and microneedle drug delivery in children: A case for disease-modifying antirheumatic drugs (DMARDs)

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ABSTRACT

Parenteral routes of drug administration have poor acceptability and tolerability in children. Advances in transdermal drug delivery provide a potential alternative for improving drug administration in this patient group. Issues with parenteral delivery in children are highlighted and thus illustrate the scope for the application of needle-free and microneedle technologies. This mini-review discusses the opportunities and challenges for providing disease-modifying antirheumatic drugs (DMARDs) currently prescribed to paediatric rheumatology patients using such technologies. The aim is to raise further awareness of the need for age-appropriate formulations and drug delivery systems and stimulate exploration of these options for DMARDs, and in particular, rapidly emerging biologics on the market. The ability of needle-free and microneedle technologies to deliver monoclonal antibodies and fusion proteins still remains largely untested. Such an understanding is crucial for future drug design opportunities. The bioavailability, safety and tolerance of delivering biologics into the viable epidermis also need to be studied.

Contents

Abbreviations: CINCA, chronic infantile neurologic cutaneous and articular; CIVAS, central intravenous additive services; DMARD, disease-modifying antirheumatic drug; i/v, intravenous; i/m, intramuscular; JIA, juvenile idiopathic arthritis; NSAID, non-steroidal anti-inflammatory drug; PK, pharmacokinetic; s/c, subcutaneous; SC, stratum corneum; TDD, transdermal drug delivery; TEWL, transepidermal water loss.

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1. Introduction

Recent European paediatric drug legislation (Anon, 2006) underlined the need to develop age-appropriate formulations. This need extends to 'easy to administer' and minimally invasive/painless drug delivery methods and devices. The parenteral route is particularly problematic in children and thus transdermal drug delivery (TDD) provides a potential alternative. As such, paediatric rheumatology patients are a pertinent population often subjected to intravenous (i/v), intramuscular (i/m) and subcutaneous (s/c) routes of drug administration and often on a long term basis. Children present with juvenile idiopathic arthritis (JIA) from 1 to 2 years of age exemplifying the need for drug delivery systems that are less painful and have less impact on daily activities. The focus of this paper is to highlight the administration related issues of parenteral (i/v, i/m and s/c) drug therapy in children and to discuss the opportunities and challenges for developing needle-free and microneedle TDD technologies to deliver disease-modifying antirheumatic drugs (DMARDs) used in paediatric rheumatology.

2. Difficulties with parenteral drug delivery in children

Some drugs need to be given parenterally due to instability and enzymatic degradation in the gut (e.g. proteins and peptides), variable oral absorption, the need for rapid onset of action or to avoid first-pass metabolism and gastrointestinal side effects (e.g. methotrexate). Consequently, i/v, i/m and s/c injections are commonly used administration routes.

The difficulty with injections is that they usually have to be administered by professionally trained staff and cause pain (Cummings et al., 1996; Gill and Prausnitz, 2007c). Patients or carers can be taught to self administer s/c injections at home, but anxiety associated with needle phobia (Broome et al., 1990) in the paediatric population can be significant. The i/v route usually involves frequent infusions requiring preparation under sterile conditions. Some of the excipients used in the formulation may also be unsuitable for younger children (Breitkreutz and Boos, 2007) as metabolic pathways are still developing. The infection risk is also higher with the i/v route compared to other routes. Furthermore, intravenous access in young children may be challenging. For example, peripheral venous access can be very difficult due to smaller veins in children. It can lead to tissue damage or extravasation and repeated cannulations for regular, repeated treatments can be a major challenge to the child, their family and healthcare professionals. Central venous access may address some of these issues, but requires general anaesthesia for insertion and removal and is associated with specific complication risks including infection. Compatibility of i/v medications with typical diluents, syringes, tubing and infusion bags also needs to be considered.

For s/c injections, in addition to needle pain and phobia, the volume administered needs to be small to avoid pain. Whilst the volume in adults should be $\leq$2 mL (Ansel et al., 2004), for children it is usually restricted to $\leq$1 mL. The s/c route is also limited to formulations that are non-irritating to the tissue and do not cause necrosis and sloughing at the injection site.

For i/m injections, children have smaller muscle mass that can affect drug delivery and absorption. Again, the volume administered will affect the pain felt and is usually restricted to 2–3 mL. Adverse effects of the i/m route commonly include persistent pain which may affect mobility, erythema and hematoma, and rarely include muscle contracture, nerve damage, abscess formation, bleeding, tissue necrosis, cellulitis and gangrene (Bergeson et al., 1982; Dewit, 2001) and thus this route is avoided in children wherever possible.

Thannhauser et al. (2009) investigated non-adherence to s/c glatiramer acetate, interferon b1a, interferon b1b and i/m interferon b1 in adolescents with multiple sclerosis. Reasons for discontinuation included intolerance to injections, side effects and the medication-peer tug-of-war, described as the psychological and social conflicts experienced by these patients in integrating the medication administration into their daily routines. For example, adolescents felt it a struggle to decide between interacting with peers or staying home to do their injections, felt unsafe to do injections in public places and felt isolated and 'not normal' due to a negative reaction of peers to injections, e.g., needle phobia. These psychosocial effects in children apply generally across disease areas where chronic medication regimes impact on daily routines.

Anecdotal evidence suggests infants as young as 5 months will react to the sight of an injection if they have had it before. Negative early experiences may lead to persistent challenges of engagement with healthcare. If children struggle, there is a risk of injury to themselves and/or their carers. In addition, the impact of hidden parental distress should be taken into consideration as needle procedures are stressful events for parents during their child's treatment (Caty et al., 1989). In severe cases of non-compliance there may be a need for play specialists or restraints.

Where parenteral products are marketed in inappropriate strengths or dose-volumes for use in children, the requirement for dose calculation, measurement of very small volumes, part-usage of vials and multiple dilutions increase the risk of medication errors (Beaney, 2010). Other safety concerns include the risk of needlestick injuries, cross-contamination and safe disposal of sharps.

There are also facility and staff resource issues to consider. The preparation of infusions of immunosuppressants and biologics require appropriate protective and contained environments as offered by central intravenous additive services (CIVAS) in hospitals, which increases workload. Even prefilled syringes for s/c or i/m injection that are not of the appropriate strength for children require decanting in such facilities to obtain the appropriate dose.

3. Challenges with current drug administration in paediatric rheumatology

Paediatric rheumatic diseases comprise a complex group of autoimmune, auto-inflammatory and musculoskeletal conditions characterised by pain, inflammation and loss of function that can lead to tissue damage and significant associated morbidity and/or mortality. Symptomatic treatment includes use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to treat pain, inflammation and stiffness. NSAIDs are usually administered orally whereas corticosteroids may be given orally, intravenously or locally by i/m or more commonly by intra-articular injection. DMARDs are aimed at suppressing disease activity, inducing and maintaining remission and so change the natural history of the disease in question.

Currently available DMARDs fall into two broad categories: chemical/synthetic immunosuppressants and biologic therapies such as monoclonal antibodies and fusion proteins which exert their effects by inhibiting pro-inflammatory cytokines or targeting cells important in the immune pathways of disease (Strand et al., 2007).

Drugs currently in use or under investigation to suppress disease activity in paediatric rheumatic conditions are discussed below in the context of patient benefit for developing needle-free or microneedle drug delivery systems. Since azathioprine, mycophenolate mofetil, hydroxychloroquine sulphate and ciclosporin are administered orally and cyclophosphamide requires a monthly i/v infusion for a short term, these drugs are considered less relevant in this context and hence not discussed.

Methotrexate is a widely used DMARD to treat JIA, juvenile dermatomyositis, systemic vasculitis, uveitis, juvenile-onset systemic lupus erythematosus and localised childhood scleroderma given once weekly by the s/c, oral or occasionally i/v routes. Associated nausea and vomiting from oral administration may lead to a significant phobia to weekly methotrexate treatment amongst children. Anticipatory nausea can occur from the day before medication until 2 4h after the dose, effectively causing 3 days of sickness for a once weekly treatment. Patients have also been reported to develop an aversion to the colour yellow (the colour of methotrexate oral liquid). Absorption may be better from the s/c route (Hoekstra et al., 2004; Tukova et al., 2009). Therefore, if oral dosing is ineffective the s/c route is preferred, but the injection stings and the associated nausea not always avoided. Regular blood monitoring for potential systemic side effects caused by methotrexate add further to the associated needle-burden of methotrexate administration which for some children becomes prohibitary. Parents have also identified methotrexate treatment as impairing their affected children's quality of life (Mulligan et al., 2008). The above factors and frequency and duration of treatment (up to 2 years and repeated in relapse) highlight methotrexate as a potential candidate for needle-free TDD.

There has been a proliferation of biological therapies available to treat inflammatory conditions in recent years. Paediatric trials have included etanercept, adalimumab, infliximab, abatacept, tocilizumab and anakinra in the treatment of juvenile idiopathic arthritis (Beresford and Baildam, 2009). However, all biological products available have to be administered by i/v or s/c injection due to oral route instability and the duration of treatment is usually long term. As newer biological agents continue to emerge and be used in JIA one of the future challenges is adapting formulations for paediatric administration (Beresford and Baildam, 2009).

Etanercept has to be administered s/c twice weekly at 0.4 mg/kg, although a weekly s/c injection at 0.8 mg/kg is also used. Injections can be cumbersome and difficult if the patient is needle phobic. Injection site reactions also commonly occur with this drug and the effect of delivering the drug into higher skin layers to reduce reactions is worthy of investigation.

Adalimumab is administered s/c every 2 weeks and is often described as painful (equated to a bee sting by adult patients). Furthermore only 40 mg prefilled syringes and pens are currently available in the UK requiring sterile decanting of 20 mg doses used in children from prefilled syringes.

Infliximab is administered as an i/v infusion and the systemic adverse effects require chlorphenamine and hydrocortisone to be administered prophylactically. The frequency of administration (initial dose, followed by 1 dose a fortnight later, then 4 weeks later and then continued either every 4 or 8 weekly as clinically indicated) and the requirement to return to hospital is inconvenient. Furthermore the time taken for sterile infusion preparation, the 2.5 h infusion delivery time, followed by a 1 h observation period make for a long and tiring visit for patients and parents and impacts on their daily activity and quality of life.

Tocilizumab – is given by i/v infusion, 2 weekly in systemic-onset JIA and 4 weekly in current trials in polyarticular course JIA; it has similar preparation and administration issues as infliximab. The infusion is given over 1 h followed by a 0.5 h observation period.

Anakinra requires daily s/c administration. It is used in systemic-onset JIA, or auto-inflammatory conditions such as chronic infantile neurologic cutaneous and articular (CINCA) syndrome.

The above is not exhaustive but illustrative of current treatment. Other molecules are under investigation, such as canakinumab currently undergoing paediatric clinical trials for systemic JIA, administered by s/c injection.

The significant challenges and limitations of the i/v and s/c routes in children with rheumatic disorders underline the importance of developing alternative drug delivery technologies including TDD systems. Physiological and technical considerations for the development of TDD systems will now be considered.

4. Skin physiology in relation to age

Numerous studies investigating the skin development process have generally focused on the first year of life (including premature birth). The stratum corneum (SC), the outermost layer of skin, which regulates water and heat loss and prevents the entry of toxins and microorganisms into the body, is also the main permeability barrier against the delivery of drugs through the skin and thus most pertinent in this context. Early histological investigations (Evans and Rutter, 1986) suggested that development of skin barrier function increased *in utero* with gestational age, reaching maturation at 34 weeks when the SC is visible and hence that full term neonates (40 weeks gestational age) are born with a barrier function comparable to adults.

However, using transepidermal water loss (TEWL) and impedance spectroscopy to correlate skin barrier maturation with gestational and postnatal age, Kalia et al. (1998) demonstrated that at 30 weeks gestational age barrier function was comparable to adult values. Furthermore, ultra low birth weight babies (23–24 weeks gestational age) took 7–9 weeks postnatally to attain adult values. SC development was not continuous but with bursts of improved barrier function seen between 1–3 weeks and 5–7 weeks postnatally. Premature exposure to a terrestrial environment acts as stimulus for rapid epidermal cell differentiation (Evans and Rutter, 1986) and barrier development (Kalia et al., 1998) and thus both gestational and postnatal age influence the state and rate of skin barrier function in premature babies (Kalia et al., 1998).

In contrast to these earlier findings regarding the age for SC maturation, Visscher et al. (2000) reported that for full term babies, SC barrier properties change markedly over the first 4 weeks after birth, including an increase in surface hydration, a decrease in TEWL under occlusion, a decrease in surface water desorption rate and a decrease in skin pH. Furthermore, Nikolovski et al. (2008) described the lack of consensus amongst co-workers and showed that barrier function, water-holding and water-transport of infant SC continued to develop through the first year of life.

Gender was not found to have a significant effect on skin pH, SC hydration, epidermal desquamation or surface roughness in full term healthy neonates (Hoeger and Enzmann, 2002).The same study confirmed previous findings that skin surface pH decreased from 6.2 to 7.5 at birth to adult values ranging between 5.0 and 5.5 by the 4th week of life. The mean pH at 3 months of age showed variation between the forearm (4.82) and buttock (5.55). Other differences in skin physiology in relation to anatomic sites need to be considered. The stratum corneum on the lower thigh area of infants

was found to be 30% thinner and the epidermis 20% thinner than in adults (Stamatas et al., 2010).

Fluhr et al. (2000) reported a significantly lower hygroscopicity and an increased cutaneous blood perfusion in a sample of children aged between 1 and 6 years compared to their parents, which could affect the pharmacokinetics (PK) of TDD and needs to be investigated. Furthermore, the effect of skin disorders should be taken into account. Depending on severity, atopic dermatitis, infections and ichthyoses may reduce the effectiveness of the SC barrier function thus enhancing TDD until the disorder improves (Williams, 2003). Whilst earlier studies demonstrated barrier dysfunction in atopic dermatitis (Aalto-Korte and Turpeinen, 1993; Ogawa and Yoshiike, 1992), a later study by Eberlein-Konig et al. (2000) found that parameters such SC hydration, TEWL and surface roughness were not significantly different in primary school children with and without atopic dermatitis, but this may be due to the lower disease severity in the children studied.

It is anticipated that children with rheumatic disease would be diagnosed between 1 and 2 years of age or later and hence not begin DMARD treatment before the end of infancy. Although the SC would be fully formed by this time, for the delivery of macromolecules using technologies that breach the SC, there is a paucity of published research on differences in deeper skin layer physiology between childhood (2–11 years), adolescence (12–17 years) and adulthood. Specific research needs for the various technologies discussed in this article are highlighted in the relevant sections.

5. Transdermal drug delivery technologies

TDD offers an attractive alternative to oral and parenteral routes to avoid palatability issues (e.g. poor taste), gastrointestinal drug degradation, first-pass metabolism, hepatotoxicity, pain on injection, needle-stick injuries, emotional trauma of injection, disease transmission and to prolong drug release, improve bioavailability and improve patient compliance. The first such system to be licensed was the transdermal 'patch' in 1979, used to deliver scopolamine for motion sickness. Subsequently, there has been a proliferation of patches on the market. However, these traditional TDD systems are limited to passively delivering drugs of low MW (<500 Da), moderate lipophilicity (log *P* 1–3), low melting point (<200 °C), aqueous solubility (>100 μg/mL) and high potency (daily dose <10 mg/day) (Williams, 2003) due to some intrinsic restrictions of the transdermal route.

Fig. 1 illustrates how advances in the development of TDD methods have enabled increased skin permeability and provided an added driving force for drug transport into the skin but the risk of damage to deeper tissues or pain has limited the applicability of some methods (e.g. chemical enhancers, iontophoresis and non-cavitational ultrasound) to deliver macromolecules (Prausnitz and Langer, 2008). Other techniques (e.g. electroporation, mechanical microporation via microneedles and thermal, radiofrequency and laser ablation) target the disruption of the SC barrier without affecting deeper tissues whereas jet injectors can be designed to penetrate the SC, epidermis or dermis. These targeted methods that overcome the SC barrier present opportunities for the transdermal delivery of large biological molecules and offer potential solutions to the challenge of adapting formulations of the new biological agents for the treatment of rheumatic conditions in children. For these patients, the most acceptable TDD systems are likely to be patches, needle-free injections and microneedles. These technologies are described and discussed in the following sections in terms of potential benefits, drawbacks, current work and research needs. Other potential technologies and synergistic combinations are also discussed.

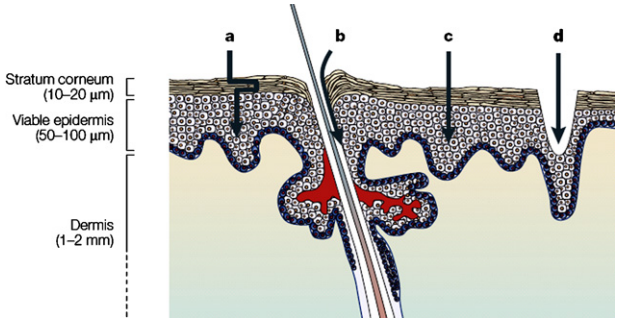

Fig. 1. Schematic representation of a cross section through human skin and potential modes of drug delivery. Stratum corneum, located on the outer surface of the skin, is a non-living layer of keratin-filled cells surrounded by a lipid-rich extracellular matrix that provides the primary barrier to drug delivery into skin. The epidermis below is a viable tissue devoid of blood vessels. Just below the dermal-epidermal junction, the dermis contains capillary loops that can take up transdermally administered drugs for systemic distribution. (a) Passive diffusion from transdermal patches, possibly in the presence of a chemical enhancer, takes place by a tortuous route across the stratum corneum, winding around cells and occurring along the interfaces of extracellular lipid bilayers. (b) Low-voltage electrical enhancement by iontophoresis can make transport pathways through hair follicles and sweat ducts more accessible. (c) High-voltage enhancement by electroporation has been shown to occur via transcellular pathways made accessible by disrupting lipid bilayers. The application of ultrasound makes pathways (a) and (c) more permeable by disorganizing lipid bilayer structure. (d) Jet injectors, microneedles, thermal poration, radiofrequency ablation and laser ablation create micron-scale holes in skin to provide pathways for drug transport.
Source: Adapted and reproduced from Prausnitz et al. (2004), with permission from Macmillan Publishers Ltd.

5.1. Transdermal patches

A transdermal patch consists of an adhesive patch incorporating a drug which is either evenly distributed within the adhesive layer, in a matrix with a full or peripheral adhesive layer or as a reservoir with a rate controlling membrane and full or peripheral adhesive layer (Hadgraft, 1996; Venkatraman and Gale, 1998; Williams, 2003). Numerous variations of these systems have also been utilised. Drug delivery after application of a patch onto the skin occurs via a combination of partitioning and passive diffusion through the SC and viable epidermis into the dermis which is rich in capillaries for systemic absorption (Williams, 2003). Transdermal patches have been used to deliver drugs such as scopolamine, fentanyl, oxybutynin and methylphenidate to children. The utility and limitations of this passive method have been previously reviewed (Brown et al., 2006; Hadgraft, 1996; Prausnitz and Langer, 2008; Tanner and Marks, 2008).

A fundamental requirement for this delivery system is that the drug candidate must be able to partition into and diffuse through the SC, which presents a substantial barrier to almost all drugs with a high molecular weight (MW). The required drug characteristics for passive transdermal delivery are described above and discussed by Guy and Hadgraft (2003) and Williams (2003). Drugs that do cross the SC need to then diffuse into the blood circulation but diffusion rates depends on MW and the concentration gradient plus macromolecules may have limited solubility in aqueous medium (Arora et al., 2008). Available physicochemical characteristics of the currently used biologics, given in Table 1, illustrate the unsuitability of these molecules for passive TDD through the SC: most have MWs 300-fold higher than the general limit of 500 Da and all are hydrophilic (negative log *P* values). Thus, methotrexate may be the only potential DMARD candidate for a patch system if designed to be used alone (i.e. without additional methods that disrupt the SC barrier). It is also worth noting that paediatric DMARD doses vary depending body weight or body surface area (Table 1), therefore, relevant PK and safety data would be required to allow

Table 1
Physicochemical and pharmacokinetic characteristics of selected DMARDs.

Drug	State	MW (Da)	log *P*[a]	pK_a[a]	Melting point (°C)[a]	Paediatric doses	Half-life[b]	Absolute bioavailability (%)[b]
Methotrexate	Solid	454[a]	−2.200	4.70	195	10–25 mg/m^2 oral, s/c or i/m weekly (1 month–18 years)[c]	Considerable variation 3–17 h; average 6–7 h	≈100
Etanercept	Liquid	150,000[b]	−0.529	7.89	–	0.4 mg/kg s/c twice weekly (4–17 years)[c]	70 h	76
Adalimumab	Liquid	148,000[d]	−0.441	8.25	–	40 mg s/c every 2 weeks (13–17 years)[c] 24 mg/m^2 s/c (max. dose 40 mg) every 2 weeks[e]	336 h	64
Infliximab	Liquid	149,100[f]	−0.441	8.25	–	3–6 mg/kg i/v every 2 weeks titrated down to every 8 weeks[e]	262 h	–
Anakinra	Liquid	17,257[a]	−0.412	5.46	–	1–2 mg/kg/day s/c daily[g]	4–6 h	95
Tocilizumab	Liquid	150,000[h]			–	8 mg/kg i/v every 2 or 4 weeks[e]	Concentration dependent, decreasing from 336 to 192 h following a dose of 8 mg/kg every 4 weeks	–

s/c: subcutaneous; i/m: intramuscular; i/v: intravenous.
[a] www.drugbank.ca/drugs/.
[b] Summary of product characteristics.
[c] British National Formulary for Children 2010–2011.
[d] www.pharmgkb.org.
[e] Doses investigated in JIA as summarised by Beresford and Baildam (2009).
[f] Klotz et al. (2007).
[g] Doses reported by Gattorno et al. (2008), Lequerre et al. (2008), Ohlsson et al. (2008).
[h] www.fda.gov/ohrms/dockets/ac/08/slides/2008-4371s1-02-Roche-core_files/frame.htm.

dose-banding into age groups and to determine optimum drug loading and release rates from patches as well as other controlled release TDD systems.

Chandak and Verma (2008) developed matrix-type methotrexate transdermal patches using hydroxypropyl methylcellulose films. They reported the drug to be compatible with the films, no skin irritation in rabbits and PK studies in rabbits supported progression to PK evaluation in humans.

As previously mentioned, the delivery of biologics, due to their size, would have to be facilitated by physical methods that overcome the SC barrier. These include the use of liquid jet injectors, powder jet injectors, microneedles, electroporation, thermal poration, dermabrasion, and laser, suction or radiofrequency ablation. Recent reviews of these technologies have already been conducted (Arora et al., 2008; Banga, 2009; Baxter and Mitragotri, 2006; Benson and Namjoshi, 2008; Brown et al., 2006; Cevc and Vierl, 2010; Kalluri and Banga, 2011b; Ogura et al., 2008; Prausnitz and Langer, 2008; Sachdeva and Banga, 2011). Consideration needs to be given to some of these technologies as favourable drug delivery options for children in line with the physicochemical properties of the drug and transdermal PK. The considerations with respect to paediatrics and potential applications in rheumatology are discussed below for relevant TDD systems.

5.2. Jet injectors

5.2.1. Liquid jet injectors

Liquid jet injectors employ a high speed jet to puncture the skin and deliver drugs without the use of needles (Arora et al., 2008). They operate using compressed gas or a spring mechanism which is used to eject a jet of liquid under pressure from the device onto the skin. The skin is penetrated by the liquid jet and hole formation continues until the velocity of the jet can no longer penetrate deeper into the skin layers and liquid dispersion occurs (Arora et al., 2008). Jet injectors have seen significant modifications in recent years, including the introduction of plastic nozzles and the development of fully disposable pre-loaded devices (Baxter and Mitragotri, 2006). However, this technology has shown variable adverse reactions and patient acceptability. For example, more injection site reactions (soreness, redness and swelling) were noted using the Biojector® device compared to a 1 in. i/m needle for delivering Hepatitis A and B vaccines (Williams et al., 2000), whilst variability in the site reactions using the Medijector II® device to deliver insulin were reported by Houtzagers et al. (1988). Whilst there is increased appeal for liquid jet injectors for the delivery of growth hormone due to the young target population (Baxter and Mitragotri, 2006), there have been mixed reports of their tolerability using the Medi-Jector® (Verhagen et al., 1995), Preci-jet 50® (Bareille et al., 1997) and Genotropin ZipTip® (Dorr et al., 2003) devices. No significant difference in pain between insulin administration by needle and liquid-jet using the Vitajet II® device was reported in a study in patients aged 9–21 years (Schneider et al., 1994).

Variability in the level of pain and local reactions during use of conventional jet injectors may be due to the limited flexibility in their settings (Arora et al., 2008). Recently, pulsed microjets that limit the penetration depth of the jets into skin and thus potentially minimise these effects have shown effective delivery of insulin to rats (Arora et al., 2007) and development of such devices may improve acceptability for children.

Liquid jet injectors have been used to deliver a range of vaccines, proteins such as insulin, growth hormone, erythropoietin and interferon, ampicillin, lidocaine, midazolam, steroids and bleomycin, as reviewed by O'Hagan and Rappuoli (2006) and Baxter and Mitragotri (2006). These jet injectors are claimed to be amenable to parenteral formulations intended for needle-based injections (Baxter and Mitragotri, 2006). However, efficacy and safety criteria need to be met and regulatory considerations are discussed later.

Factors affecting drug penetration that require further investigation are mechanical properties of the skin, injection volume and the distance between the injector orifice and skin when the device is actuated (stand-off distance) (Arora et al., 2008). Determination of the size and shape of the jet induced hole in skin, development

of predictive models that require an understanding of fluid dynamics of the skin, skin failure mechanisms and fluid dispersion into tissue is also needed (Baxter and Mitragotri, 2006). Importantly, these factors need to be investigated in relation to age. The stability of drugs in jets needs to be established as shear forces are higher compared to needle based injections. A clear understanding of the pain caused by this administration method and local reactions is needed and whether they are drug, formulation or device specific.

5.2.2. Powder jet injectors

Powder jet injectors for the delivery of biological macromolecules as dry powder formulations provide the advantage of ease of storage and improved stability compared to liquid formulations (Amorij et al., 2008). These injectors deliver drugs in dry powder form into the superficial layers of skin. When actuated, a flow of compressed gas carries the drug particles out of the device nozzle, which upon impacting the skin, penetrate the SC with a significant proportion reaching the viable epidermis. As some particles are retained in the SC, impact velocity, particle size and particle density become important design parameters in determining the depth of penetration into the skin layers (Arora et al., 2008; Kendall et al., 2004a). In addition, increasing relative humidity and temperature have been shown to increase penetration depth (Kendall et al., 2004b). However, the final particle location can be affected by inter-individual differences in skin layer thickness (Kendall et al., 2004a).

Reports have suggested that pain-free delivery can be achieved, but mild erythema, hyper-pigmentation, flaking and discolouration at the injection site following administration of dry powder DNA vaccines to adults have been recorded, although most reactions resolved within 1 month (Arora et al., 2008). It is unknown whether repeated administration would result in persistent formulation or device-related adverse effects. If injection site reactions are related to the excipients within a liquid formulation and not the drug itself, they may be reduced through reformulating to a powder for jet injection. The authors are not aware of any products currently in advanced development using this technology.

The disadvantages associated with the development of jet injectors are the cost of the technology and the noise on activation of the devices, which may replace the fear of needles in young children. Furthermore, strict specifications for the gas pressure and nozzle geometry of the device and for the particle size, shape, morphology and density may pose technical challenges.

5.3. Microneedles

A microneedle TDD system consists of hundreds of microfabricated microneedles over a base substrate, which can pierce the SC to create transient pathways and enable delivery of small and macromolecules (Tanner and Marks, 2008). No infections, little skin irritation (Matriano et al., 2002) and no bleeding (Martanto et al., 2004) have been associated with the use of microneedles. In comparison to s/c injections, drug delivery using microneedles is relatively painless due to their small size reducing the likelihood of stimulating nerves and creating a painful sensation (Prausnitz, 2004; Sachdeva and Banga, 2011). However, the design of microneedles can affect the level of pain felt and increasing microneedle length and number have been directly correlated to pain (Gill et al., 2008). Nevertheless, the pain caused by microneedles was significantly lower than that from using a hypodermic needle (Gill et al., 2008; Haq et al., 2009). Microneedle technology enables the delivery of high MW and highly water-soluble drugs and the current state-of-the-art has recently been published (Cleary, 2011). Also, in a survey of public and healthcare professional opinions on introducing microneedles into clinical practice, the advantages over parenteral routes were recognised and welcomed, with concerns centring around efficacy, safety, convenience and cost issues currently faced in development (Birchall et al., 2011).

The type of microneedle design influences the delivery mechanism. Whilst solid microneedles can be pressed or scraped into the skin to increase permeability in preparation for subsequent drug delivery via transdermal patch or topical formulation, biodegradable or water-soluble polymer based microneedles have been fabricated for depot controlled release of drugs (Park et al., 2006). Four types of microneedle design have been reported (Arora et al., 2008; Prausnitz, 2004; Sachdeva and Banga, 2011), as shown in Fig. 2:

- Solid microneedles for piercing the skin prior to drug application.
- Solid microneedles coated with drug for rapid dissolution in skin.
- Dissolving polymeric microneedles that are drug-free or encapsulated with drug for rapid or controlled release.
- Hollow microneedles for injection of drug solution.

The application of these designs in delivering a range of molecules have been reviewed by Arora et al. (2008), Kalluri and Banga (2011b) and Sachdeva and Banga (2011) and include proteins and vaccines. Gill and Prausnitz (2007a) specifically investigated factors affecting the microneedle coating process and optimised them to successfully deliver a range of molecules into porcine cadaver skin. They also optimised a selection of coating formulations for hydrophilic and hydrophobic molecules and showed uniform coating of microneedles with insulin and bovine serum albumin using a dip-coating method (Gill and Prausnitz, 2007b). Chen et al. (2009) demonstrated the potential of a gas-jet drying coating technique for densely packed microneedles unsuitable for dip coating, delivering ovalbumin vaccine into skin within 3 min of microneedle insertion and producing an immune response comparable to i/m injection in mice. Dissolving microneedles offer inexpensive material and production costs, use biodegradable polymers with known safety profiles and remove the risk of leaving sharp residuals from silicon or metal microneedles in the skin (Migalska et al., 2011). The stability on encapsulation and timely dissolution has been reported for macromolecules including insulin (Ito et al., 2006a; Migalska et al., 2011), recombinant human growth hormone and desmopressin (Fukushima et al., 2011), inactivated influenza vaccine (Sullivan et al., 2010) and erythropoietin (Ito et al., 2006b). Using stainless steel hollow microneedles for intradermal delivery, Harvey et al. (2011) successfully delivered human doses of etanercept to swine without detrimental effects on drug stability due to shear degradation. The time to maximum concentration was 71% lower and the maximum blood concentration was 193% higher compared to the s/c route. The stability, sterility and safety (containment) of biologics in potential reservoirs used for hollow microneedles must be assessed.

Microneedle penetration performance depends mainly on the material used, needle height, shape and density, spacing between needles, tip dimensions (e.g. radius of curvature), base diameter and differences in skin elasticity and thickness between populations and anatomical regions (Al-Qallaf and Das, 2009; Sachdeva and Banga, 2011; Singh et al., 2011). Whilst the thickness of the epidermis strongly influences permeability and should be considered when developing solid microneedle systems, skin permeability is a function of microneedle length in hollow microneedle systems since the drug moves through the needle bore rather than from the needle surface (Al-Qallaf and Das, 2009). In order to optimise microneedle geometry to improve transdermal drug permeability to levels of interest, Al-Qallaf and Das (2009) developed an optimisation algorithm for solid and hollow microneedles.

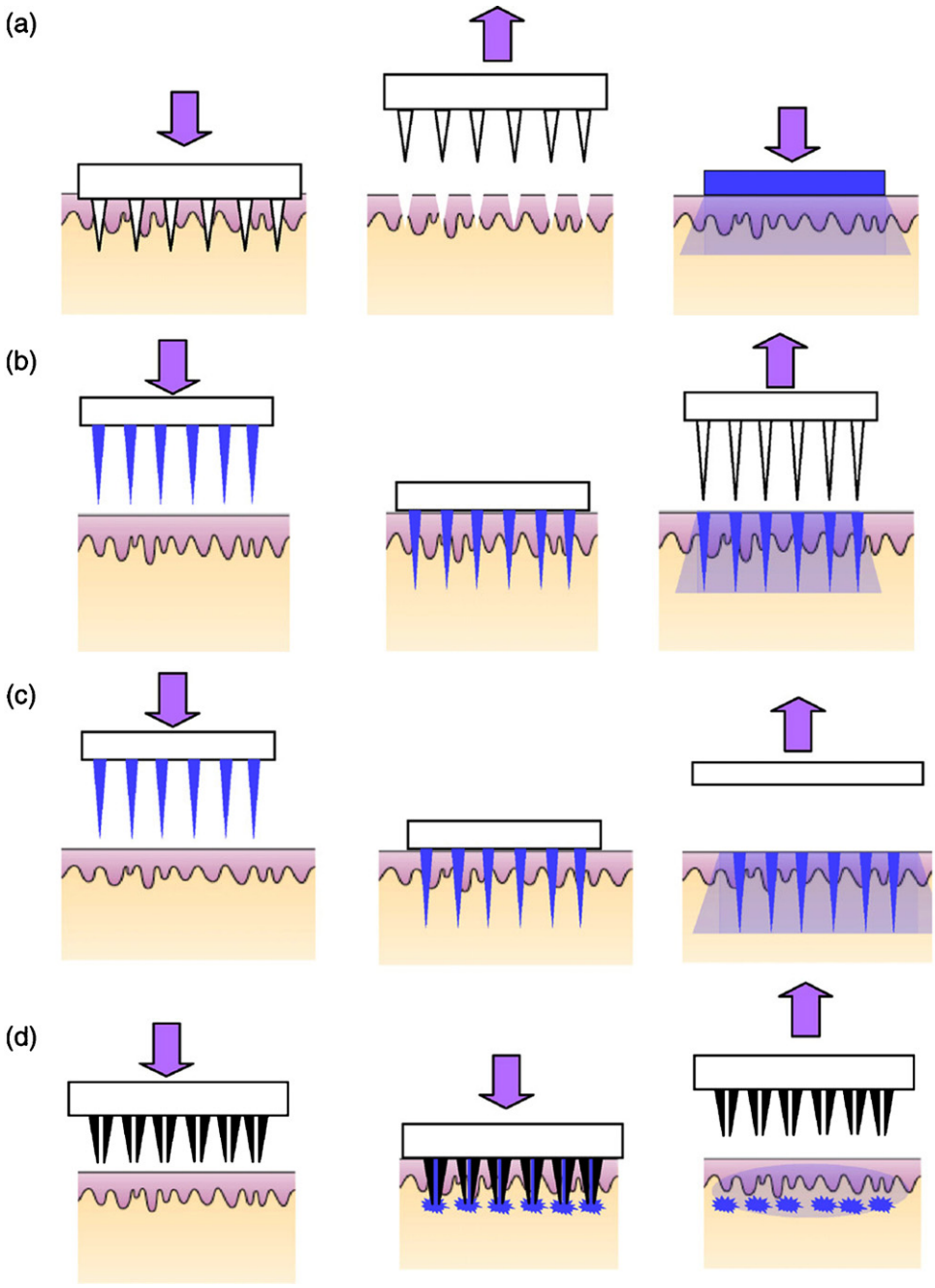

Fig. 2. Schematic of drug delivery using different designs of microneedles: (a) solid microneedles for permeabilizing skin via formation of micron-sized holes across stratum corneum. The needle patch is withdrawn followed by application of drug-containing patch. (b) Solid microneedles coated with dry drugs or vaccine for rapid dissolution in the skin. (c) Polymeric microneedles with encapsulated drug or vaccine for rapid or controlled release in the skin. (d) Hollow microneedles for injection of drug solution. *Source*: Reproduced from Arora et al. (2008), with permission from Elsevier.

Regardless of the geometry and physical properties of the microneedles, the accuracy and reproducibility of their penetration depth into the skin is crucial to limit inter and intra-individual variability in dose response. Achieving this reproducibility in penetration depth is hindered by the inherent elasticity and irregular surface of the skin (Singh et al., 2011). Penetration force therefore needs to be controlled by using a suitable applicator that also limits deformation of the skin at the application site (e.g. by stretching or pulling the skin). Singh et al. (2011) have reviewed current patents on applicator designs intended to provide uniform and reproducible penetration of microneedle arrays into skin. Pertinent to the scope of this review is the need for ease of use of such applicators for healthcare professionals, convenient carriage (e.g. designs similar to insulin pen devices), simplicity for self administration by patients of various ages and educational backgrounds, reusability and low cost (Singh et al., 2011).

The drug formulation is vital to successful drug delivery and requires early consideration for optimisation in relation to the type of microneedle used and whether rapid or controlled release is required. Formulation factors affecting transdermal flux and potential methods to enhance flux are discussed by Milewski et al. (2010).

Despite the potential for microneedle delivery systems, some limitations are associated with their use. Using uncoated solid microneedles would still require a patch formulation for drug delivery after skin is disrupted adding to the complexity and cost. Coated microneedles can only deliver a very small drug dose, typically up

to 1 mg on a patch size ≈10–20 cm^2 (Gill and Prausnitz, 2007b). For dissolving polymer microneedles, high drug loads may compromise mechanical strength and the formulation step requires high temperatures which could denature some proteins, but preparation at ambient temperatures has recently been achieved (Donnelly et al., 2011; Lee et al., 2008; Migalska et al., 2011; Sullivan et al., 2008). Hollow microneedles are technically difficult and expensive to fabricate and can be blocked by tissue debris during insertion. Gonnelli and McAllister (2009) have patented a design with movable plugs to address this problem. Furthermore, high flow rates and infusion volumes through hollow microneedles can cause backflow and skin leaking and these limits still need to be investigated (Roxhed et al., 2008). The holes formed in the SC may also close relatively quickly or the microneedle material may seal the holes, thus limiting the drug delivery (Donnelly et al., 2009). The pore closure time after microneedle insertion and removal is a crucial factor in maintaining drug delivery (Milewski et al., 2010). Microneedles may require insertion by hand or high velocity application which could damage them. Thus, effective insertion into the skin is dependent on the geometry and physical properties of the needles (Davis et al., 2004) which could add a level of complexity in designing coated microneedles.

5.4. Other techniques

Enhancement of percutaneous penetration of peptides has been achieved by using chemical permeability enhancers which increase drug diffusivity via SC lipid fluidisation, chemical modification of peptides to make them more lipophilic, encapsulation (e.g. into liposomes) and addition of facilitating peptide sequences, but these approaches are of limited value for larger peptides and proteins (Benson and Namjoshi, 2008; Kalluri and Banga, 2011b).

Iontophoresis is a technique that uses a small voltage to push charged molecules into the skin but because this method does not disrupt the SC barrier it is unlikely to be able to deliver larger macromolecules (>7000 Da) when used alone (Prausnitz and Langer, 2008; Tanner and Marks, 2008). This technique also requires the drug to have good aqueous solubility. Iontophoresis may be of value in the delivery of methotrexate, either alone (Alvarez-Figueroa et al., 2001; Singh and Singh, 2001) or in combination with chemical enhancers (Prasad et al., 2009) and recent reviews of this technique have been published (Delgado-Charro, 2009; Semalty et al., 2007). Iontophoresis could be considered for delivering larger macromolecules if used in combination with physical barrier disruption methods and is discussed under combination methods. For proteins, the isoelectric point and final pH of the formulation will then become important determinants for successful delivery (Kalluri and Banga, 2011b).

Low-frequency sonophoresis utilises ultrasound (20–100 kHz) to increase the permeability of the SC thus enabling the delivery of macromolecules. The ultrasound induces acoustic cavitation (the formation and collapse of gas bubbles) in the liquid coupling medium between the ultrasound transducer and the skin. The collapse of air bubbles results in the emission of shock waves and/or high velocity microjets against the skin surface which disrupt the phospholipid bilayers in the SC (Tezel and Mitragotri, 2003). The ultrasound and drug can be applied simultaneously to the skin or the skin can be pre-treated with ultrasound prior to drug application. For simultaneous sonophoresis, drug transport enhancement decreases when the ultrasound is turned off and the patient would require a wearable ultrasound device (Ogura et al., 2008). Using the pre-treatment method, maintenance of enhanced skin permeability in human volunteers has been demonstrated for approximately 15 h, returning to baseline permeability in 20 h (Kost et al., 2000). However, very short pre-treatments and low intensities are unlikely to be sufficient to deliver larger macromolecules (Benson and Namjoshi, 2008) and higher ultrasound parameters need to be investigated for tolerability to deliver proteins and peptides. The devices previously used (e.g. SonoPrep®, Sontra Medical Corporation, USA) were large and inconvenient to transport but a more compact design (Prelude® SkinPrep System, Echo Therapeutics, USA) has been patented. *In vitro* permeability of insulin, interferon γ and erythropoietin across human cadaver epidermis has been shown (Mitragotri et al., 1995) and animal studies have demonstrated physiological responses to insulin delivered by this method (Park et al., 2008a, 2007). Whilst research around miniaturisation of devices advances, better calibration of ultrasound emitted, effect of operational parameters and formulation on permeability and drug stability and the biological effects of sonophoresis require further work (Rao and Nanda, 2009).

Electroporation involves the application of intense electrical charges to create small pores in the phospholipid bilayer of the SC (Tanner and Marks, 2008), but there have been few clinical studies of this technology and patient tolerance of the associated pain is largely unknown (Benson and Namjoshi, 2008). At present, the authors are not aware of this technology being under active development.

Thermal poration is a method that uses pulsed heat to form aqueous pathways across the SC by disruption of the lipid structure and vaporisation of keratin within the SC without damaging deeper skin layers (Park et al., 2008b). A system utilising this method has been patented (PassPort Patch®, Altea Therapeutics Corporation, USA) (Eppstein et al., 2004) and Phase I and II studies for the delivery of insulin have been completed. Preclinical and clinical studies for a range of other molecules have also been conducted or are in progress (Banga, 2009).

Development to clinical trials has also been reached for drug delivery using radiofrequency thermal ablation (Viador® [previously Viaderm®], TransPharma Medical Ltd, Israel). This technique causes ionic vibrations within skin cells leading to localised heating and cell ablation (Banga, 2009) and thus forms microchannels in the SC through which drugs can diffuse. The Viador® system is currently undergoing clinical trials for three drugs: human parathyroid hormone (1–34) for the treatment of osteoporosis in collaboration with Eli Lilly currently in Phase 2b; a glucagon 1 like peptide agonist for the treatment of type II diabetes that has completed phase 1b; and calcitonin for musculoskeletal disorders that has completed Phase 1.

Erbium:yttrium–aluminium–garnet (Er:YAG) laser light used in cosmetic and plastic surgery to resurface skin has been shown to increase the permeability of macromolecules (Fang et al., 2004). Microchannels in the epidermis are created by rapid evaporation of water on the skin surface. Two devices have been launched for intra-epidermal drug delivery, the Painless Laser Epidermal System technology (P.L.E.A.S.E.®, Pantech Biosolutions AG, Liechtenstein) and the Epiture Easytouch® technology (Norwood Abbey, Australia) for which clinical studies have shown good tolerability (Kalluri and Banga, 2011b).

5.5. Combination methods

Whilst most of the techniques discussed in the previous section may have limited use in enhancing transdermal delivery of macromolecules such as DMARDs when used in isolation, the combination of two or more methods may have synergistic effects, although it can be difficult to predict which combinations will be optimum for each drug (Benson and Namjoshi, 2008). Various combinations of ultrasound, electroporation and iontophoresis have been studied, as reviewed by Prausnitz et al. (2004) and Kalluri and Banga (2011b). An *in vitro* investigation using porcine skin found that the combination of electroporation prior to iontophoresis increased the transdermal flux of human parathyroid hormone

up to 10 times greater than electroporation alone (Medi and Singh, 2003). Badkar et al. (2007) combined thermal poration with iontophoresis to enable the delivery of interferon alpha 2b in hairless rats. Also, microneedle poration prior to iontophoresis has been shown to enhance the skin permeation of high MW compounds (Katikaneni et al., 2009; Wu et al., 2007). Vemulapalli et al. (2008) demonstrated that soluble maltose microneedles used to create microchannels in skin resulted in a 25-fold enhancement in the iontophoretic delivery of methotrexate in rats. The safety and patient tolerability of such combination therapies are still to be established but they offer potential for effective delivery (Benson and Namjoshi, 2008). Regulatory approval challenges and the costs associated with commercialisation also need to be considered.

6. Regulatory and further research considerations

Some general scientific criteria apply to all transdermal delivery systems and are discussed by Shah (2003).

Particular points to note are:

- TDD systems are considered controlled release dosage forms and should demonstrate such features *in vivo* and be reproducible.
- If the drug is already marketed as different dosage forms then comparative bioavailability needs to be determined.
- The required bioavailability and PK need to be defined and different administration sites should be investigated to optimise delivery and reproducibility.
- Transdermal safety studies should include skin irritation, cutaneous toxicity and sensitivity and contact photodermatitis.
- For efficacy, clinical studies on bioavailability and *in vitro* release studies should be performed.

Specifically;

For patch systems, skin irritation study data need to be provided if using unapproved excipients. Selected adhesives and patch material should have low allergenic potential to avoid irritation and subsequent infection. Babies and children below the age of 8 years are generally considered to be more susceptible to skin irritation (Patil and Maibach, 1994). Mapping the bioavailability from different application sites is important, particularly those sites (e.g. scapular area) used to prevent removal of patches by children (Gonzalez et al., 2009). A surplus drug load is typically required for patch systems to reach and maintain a therapeutic release rate during the intended drug delivery period. However, between 10% and 95% of the initial amount could remain within the patch after the intended delivery period, which raises safety concerns about inadvertent exposure to the patient, parent, siblings, healthcare professionals and pets. In response, the FDA has released draft guidance recommending that the residual drug load be minimised (and justified in the regulatory application) (FDA, 2010), which is particularly important for developing patch systems as components of potential combination techniques for delivering DMARDs, considering their toxicity profiles.

Penetration enhancers are themselves absorbed therefore their fate in the body and mechanism of action needs to be described (Shah, 2003) and toxicity ascertained. Dose flexibility is an important issue for children and patches may need to be manipulated (i.e. cut) to obtain the appropriate dose. This issue should been borne in mind when designing a patch that may be used in a wide paediatric age range as well as adults. A patch presentation with perforated segments could provide valuable flexibility when dose banding into age groups or body weights.

For injector systems, draft FDA guidance draws attention to consideration of age, gender and the range of tissue characteristics of the target population. Factors such as manual dexterity in arthritic conditions and ease of operation for self administration are also mentioned and pertinent in older children who may self administer their medicines. Compatibility of the drug product with device materials and sterility of the device–drug product must also be demonstrated (FDA, 2009). Baxter and Mitragotri (2006) described the research needs for liquid jet injectors and it is hoped that the development of predictive models will take into account the paediatric population.

Only a limited number of microneedle systems have been clinically studied and to date have mainly been of the solid metal type (either coated with drug or uncoated), and it has been suggested that this could be due to the difficulty in proving uniformity of doses for the low volumes delivered from hollow microneedles to gain regulatory approval (Cevc and Vierl, 2010). The lifetime of the pores created by the microneedles used will determine how effectively a dose is delivered and the risk of irritation and infection. Pore closure depends on microneedle type, length, cross-section, density and whether the application site is occluded (Kalluri and Banga, 2011a) and therefore needs to be established for specific product applications. Furthermore, immune reactions and other toxicities to microneedle fabrication materials need to be assessed.

The effect of repeated penetration of the skin using physical systems needs to be established for long term safety as well as the extent of product and patient dependent skin immunogenicity caused by biologics (Strand et al., 2007). Inter and intra-individual differences in PK that will affect efficacy and toxicity also require consideration. Drug metabolism can occur in the viable epidermis and may vary depending on the site of administration, both of which can affect bioavailability and inter- and intra-individual variability (Farahmand and Maibach, 2009). Schiffer et al. (2003) showed that human epidermis contains active transporters involved in drug transport and any clinical implications for transdermal delivery of DMARDs needs further investigation including the effect of age on the maturity of such transport systems.

7. Conclusion

Given the long standing difficulties associated with drug administration, compliance and effects on daily life in children, there is a strong argument to develop needle-free and microneedle transdermal delivery systems for DMARDs in paediatric rheumatology from a patient perspective. Whilst such technologies continue to develop and become more sophisticated, their ability to deliver monoclonal antibodies and fusion proteins still remain largely untested. As the global market for biologics continues to increase rapidly, such an understanding is crucial for future drug design opportunities. The bioavailability, safety and tolerance of delivering biologics into the viable epidermis also need to be studied.

Conflicts of interest

There are no conflicts of interest.

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