Advanced Drug Delivery Reviews 103 (2016) 144–156

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy☆

Andrew Owen [a], Steve Rannard [b]

[a] Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, 70 Pembroke Place, University of Liverpool, Liverpool L693GF, UK
[b] Department of Chemistry, Crown Street, University of Liverpool, L69 3BX, UK

ARTICLE INFO

Article history:
Received 9 January 2016
Received in revised form 10 February 2016
Accepted 12 February 2016
Available online 23 February 2016

Keywords:
Nanomedicine
Formulation
Sustained-release
Time-release
Controlled-release
Extended-release
Drug delivery
Pharmacokinetics

ABSTRACT

Advances in solid drug nanoparticle technologies have resulted in a number of long-acting (LA) formulations with the potential for once monthly or longer administration. Such formulations offer great utility for chronic diseases, particularly when a lack of medication compliance may be detrimental to treatment response. Two such formulations are in clinical development for HIV but the concept of LA delivery has its origins in indications such as schizophrenia and contraception. Many terms have been utilised to describe the LA approach and standardisation would be beneficial. Ultimately, definitions will depend upon specific indications and routes of delivery, but for HIV we propose benchmarks that reflect perceived clinical benefits and available data on patient attitudes. Specifically, we propose dosing intervals of ≥1 week, ≥1 month or ≥6 months, for oral, injectable or implantable strategies, respectively. This review focuses upon the critical importance of potency in achieving the LA outcome for injectable formulations and explores established and emerging technologies that have been employed across indications. Key technological challenges such as the need for consistency and ease of administration for drug combinations, are also discussed. Finally, the review explores the gaps in knowledge regarding the pharmacology of drug release from particulate-based LA injectable suspensions. A number of hypotheses are discussed based upon available data relating to local drug metabolism, active transport systems, the lymphatics, macrophages and patient-specific factors. Greater knowledge of the mechanisms that underpin drug release and protracted exposure will help facilitate further development of this strategy to achieve the promising clinical benefits.

Contents

1. Introduction . . . 145
2. The conceptual basis for long-acting drug delivery of antiretroviral drugs . . . 146
   2.1. The key need to consider potency for antiretroviral long-acting medicines . . . 146
   2.2. A need for standardised nomenclature for long-acting delivery? . . . 146
   2.3. The importance of route of delivery in achieving the long-acting strategy . . . 148
3. Technologies that have been clinically successful for LA delivery . . . 148
   3.1. Solution-based injections . . . 148
   3.2. Suspension-based injections . . . 149
      3.2.1. Drug particle suspensions . . . 149
      3.2.2. Microparticle/microsphere suspensions . . . 149
4. Emerging technologies for LA formulation . . . 149
   4.1. Nanoparticle suspensions . . . 149
   4.2. Injectable monoliths . . . 149
   4.3. *In situ*-forming depots/implants . . . 149
   4.4. Microneedle delivery . . . 150
5. Technological challenges for LA delivery . . . 150
   5.1. Drug combinations . . . 150
   5.2. "Syringeability" . . . 150
   5.3. Depot consistency, shape and size . . . 150

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "HIV/AIDS_dasNeves_Sarmento_Sosnik"

http://dx.doi.org/10.1016/j.addr.2016.02.003
0169-409X/

5.4. Formulation sterility and manufacturing . . . 150
6. Gaps in knowledge regarding the pharmacology of solid drug nanoparticle LA injectables . . . 150
6.1. A role for drug transporters and metabolic enzymes in LA bioavailability? . . . 151
6.2. The putative role of the lymphatics in LA bioavailability? . . . 151
6.3. A role for macrophages in nanoparticle bioavailability? . . . 152
6.4. A role for endocytosis in nanoparticle permeation across capillary endothelium? . . . 152
6.5. Patient factors of putative importance in LA inter-patient variability . . . 152
7. Summary and conclusions . . . 153
Competing financial interests . . . 153
Acknowledgements . . . 153
References . . . 153

1. Introduction

The HIV/AIDS epidemic remains a major public health threat and approximately 36.9 million [34.3 million–41.4 million] people worldwide are estimated to be infected. In 2014, AIDS claimed an estimated 1.2 million [980,000–1.6 million] lives globally, with 2 million [1.9 million–2.2 million] people being newly infected in the same year. Worldwide, around 15.8 million people were accessing antiretroviral therapy in June 2015, constituting ~41% of adults and ~32% of children infected with the virus [1]. Antiretroviral therapy (ART) currently involves co-administration of drugs to simultaneously inhibit multiple viral targets, maximising inhibition of viral replication whilst minimising drug resistance. To date, 6 classes of antiretroviral drugs are available: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 antagonists and integrase inhibitors (INIs). Although ART has led to a decline in mortality and morbidity, therapeutic failure occurs in an estimated 8% of treatment naïve and 33% of treatment experienced patients [2]. Antiretroviral drugs also have clinical application in the prevention of HIV infection, and pre-exposure prophylaxis (PrEP) strategies have been developed for subjects at high risk of acquiring the infection. Several factors contribute to heterogeneity in the response to antiretroviral agents, such as viral characteristics, immunological status, and pharmacokinetic variability to drug exposure. Currently available formulations necessitate lifelong, daily dosing and suboptimal adherence places patients at risk of treatment failure and low rates of protection for PrEP [3].

Recently, two antiretroviral drugs have entered clinical development as long-acting (LA) injectable depot formulations. The first of these, developed by Janssen is rilpivirine LA (Edurant®) [4–6] and the second, developed by ViiV Healthcare is cabotegravir LA [7,8]. Both of these medicines are based upon the same nanotechnology that generates solid drug nanoparticle (SDN) suspensions via the process of wet bead milling (also known as nanomilling; see also Section 4.1 below). LA injectable formulations have previously been developed and licenced for other indications such as contraception and schizophrenia (Table 1) [9–11]. The advent of the HIV LA medicines has been greeted with great excitement within the scientific, clinical and patient communities. In the short term, since only single agent LA medicines will be available, the largest impact is likely to be made by their deployment in PrEP [12]. However, it is hoped that the arrival of these medicines will spur further development of fully LA regimens for the treatment

Table 1
Comparison of selected clinically-available long-acting injections and candidate injections under clinical development.

Technology	Drug name	Route	Dosing interval	Condition	Clinical depot volume
Suspension-based					
Solid drug particle	Medroxyprogesterone acetate	SC	3 monthly	Hormone therapy	0.65 mL
Solid drug particle	Medroxyprogesterone acetate	IM	3 monthly	Hormone therapy	1 mL
Solid drug particle	Olanzapine	IM	2–4 weekly	Schizophrenia	Max. 2.7 mL
Solid drug particle	Paliperidone palmitate	IM	1 monthly	Schizophrenia	Max. 1.5 mL
Solid drug particle	Paliperidone palmitate	IM	3 monthly	Schizophrenia	Max. 2.7 mL
Microparticle/microsphere	Somatropin	SC	2–4 weekly	Hormone therapy	Max. 1.5 mL
Microparticle/microsphere	Leuprolide acetate	IM	1–3 monthly	Prostate cancer	1.5 mL
Microparticle/microsphere	Naltrexone	IM	1 monthly	Alcohol dependence	4 mL
Microparticle/microsphere	Risperidone	IM	2 weekly	Schizophrenia	2 mL
Solid drug particle (undergoing human trials)[a]	Cabotegravir	IM	1 quarterly[a]	HIV therapy and PreP	2 × 2 mL split[a]
Solid drug particle (undergoing human trials)[a]	Rilpivirine	IM	1 monthly[a]	HIV therapy and PreP	2 × 2 mL split[a]
Solution-based					
Oil-based	Flupenthixol decanoate	IM	2–4 weekly	Schizophrenia	Max. 2 mL
Oil-based	Zuclopenthixol decanoate	IM	2–4 weekly	Schizophrenia	Max. 3 mL
Oil-based	Testosterone cypionate	IM	2–4 weekly	Hormone therapy	Max. 1.5 mL
Oil-based	Estradiol valerate	IM	1 monthly	Hormone therapy	Max. 1 mL
In-situ implant	Leuprolide acetate	SC	1–6 monthly	Prostate cancer	0.375 mL
Early stage solution-based immunotherapies					
Aqueous concentrated protein (undergoing human trials)[a]	CCR5 Monoclonal Antibody (PRO-140)	SC	1–2 weeks[a]	HIV	2 × 1 mL split[a]
Aqueous concentrated protein (undergoing human trials)[a]	Broadly neutralising monoclonal antibody (VRC01)	SC	3–4 weekly[a]	HIV	TBD
Aqueous concentrated protein (undergoing human trials)[a]	Broadly neutralising monoclonal antibody (VRC01)	IV	3–4 weekly[a]	HIV	NA[b]
Aqueous concentrated protein (undergoing human trials)[a]	Anti-CD4 binding site monoclonal Antibody (3BNC117)	IV	1 monthly[a]	HIV	NA[b]

[a] Note that since these formulations are currently still in clinical development, dosing interval and volume should be considered subject to change.
[b] Intravenous infusions have shown long-acting benefits but are not considered depot injections.