The Pharmacology of PEGylation: Balancing PD with PK to Generate Novel Therapeutics

C. SIMONE FISHBURN

Nektar Therapeutics, 150 Industrial Road, San Carlos, California 94070

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ABSTRACT: Conjugation of macromolecules to polyethylene glycol (PEG) has emerged recently as an effective strategy to alter the pharmacokinetic (PK) profiles of a variety of drugs, and thereby to improve their therapeutic potential. PEG conjugation increases retention of drugs in the circulation by protecting against enzymatic digestion, slowing filtration by the kidneys and reducing the generation of neutralizing antibodies. Often, PEGylation leads to a loss in binding affinity due to steric interference with the drug–target binding interaction. This loss in potency is offset by the longer circulating half-life of the drugs, and the resulting change in PK–PD profile has led in some cases to enabling of drugs that otherwise could not be developed, and in others to improvements in existing drugs. Thus, whereas most approaches to drug development seek to increase the activity of drugs directly, the creation of PEGylated drugs seeks to balance the pharmacodynamic (PD) and pharmacokinetic properties to produce novel therapies that will meet with both increased efficacy and greater compliance in the clinical setting. This review examines some of the PEGylated drugs developed in recent years, and highlights some of the different strategies taken to employ PEG to maximize the overall PK–PD profiles of these compounds. J Pharm Sci 97:4167–4183, 2008

Keywords: biotechnology; conjugation; drug delivery; macromolecular drug delivery; PEGylation; pharmacokinetics/pharmacodynamics; renal clearance

INTRODUCTION

Polyethylene glycol (PEG)-conjugated drugs first appeared on the pharmaceutical scene in 1990 with the FDA approval of Adagen® (pegademase: PEGylated adenosine deaminase), as enzyme replacement therapy for patients with severe combined immunodeficiency disease (SCID), an inherited disorder in which deficiency of adenosine deaminase causes accumulation of metabolites and prevents lymphocyte maturation. The approval of Adagen followed more than a decade of research, precipitated by the first description of protein PEGylation by Abuchowski et al.[1] which documented the ability of PEG to prolong the half-life and reduce the immunogenicity of a conjugated protein. When applied to adenosine deaminase to produce pegademase, the technology yielded a drug that enabled twice-weekly intramuscular injections to replace multiple blood transfusions, and, by avoiding the transfusion-associated risks of viral infection and iron overload, provided both a better pharmacological profile and a considerable improvement in convenience for patients.

The following years saw the approval of additional PEGylated therapeutics for a number of prevalent conditions including Hepatitis C,

Correspondence to: C. Simone Fishburn (Telephone: 650-631-3482; Fax: 650-631-3150; E-mail: sfishburn@nektar.com)

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chemotherapy-associated neutropenia and leukemia (Tab. 1). Several more PEG-conjugated compounds are currently in clinical and preclinical development, reflecting the emergence of this platform as a dominant strategy for enabling or improving macromolecule drugs.

The currently approved PEGylated products are all macromolecules that, between them, cross a number of therapeutic classes, including oncology, metabolic diseases and infectious diseases. The first five approved products were proteins or peptides; the most recently approved, Macugen® (pegaptanib), is an RNA aptamer, while studies on PEG-conjugates of small molecules such as the α4β1 integrin inhibitor demonstrate that the technology can extend beyond biologics and macromolecules.[2] Furthermore, clinical and preclinical studies have been reported which use PEG to make prodrugs for small molecules such as irinotecan,[3,4] doxorubicin[5–7] and camptothecin.[8,9]

Pharmacodynamic (PD) properties of a drug can be measured at the molecular level by parameters such as receptor binding affinity or enzyme activity. While PEG characteristically prolongs the plasma circulating time of a drug, a seminal PK parameter, this often comes at the expense of reduced binding affinity for the target receptor or enzyme. Thus PEG operates to alter the balance between pharmacodynamic and pharmacokinetic properties, compensating for reduction in binding affinity by extension of systemic exposure (Fig. 1). The earlier PEGylated conjugates aimed simply to use PEG to increase systemic exposure of the drug or reduce adverse reactions, without optimizing the effect on potency. More recent approaches, however, integrate the pharmacological properties of the drug and of PEG to minimize the loss of potency while maximizing exposure.

This review will: (i) describe the pharmacological properties of PEGylated drugs, (ii) highlight two case-studies, Somavert® (pegvisomant) and PEGASYS® (peginterferon-α2a), and (iii) analyze some of the different classes of drug that can benefit from PEGylation, to demonstrate how incorporating PEG conjugation into the design of a drug is emerging as an effective strategy for improving or enabling novel therapeutics.

PHARMACOLOGICAL PROPERTIES OF PEGYLATED DRUGS

PEG polymers are composed of repeating units of ethylene glycol, which can be produced as linear or branched chains, with functional groups at one or more termini to enable a variety of conjugation possibilities (Fig. 2). Chemical strategies for conjugating PEG to macromolecules are beyond the scope of this review and have been described in detail recently.[8,10] Further diversity for PEG conjugation arises from the use of either stable or hydrolyzable linkages, the latter resulting in the generation of pro-drugs. In both cases, the conjugated molecule benefits from the pharmaceutical properties of PEG, which include increased solubility, stability over a wide range of temperature and pH, and high mobility in solution.[11] However, whereas for prodrugs the activity lies in the released parent molecule, stable conjugates constitute a new active species. This new molecule possesses different pharma-

Table 1. FDA Approved PEGylated Drugs

Commercial Name	Drug Name	Parent Drug	PEG Size (Da)	Indication	Year of Approval
Adagen®	Pegadamase	Adenosine deaminase	5000	SCID[d]	1990
Oncaspar®	Pegaspargase	Asparaginase	5000	Leukaemia (ALL[e], CML[f])	1994
PEG-INTRON®	Peginterferon-α2b	IFN-α2B	12000	Hepatitis C	2000
PEGASYS®	Peginterferon-α2a	IFN-α2A	40000	Hepatitis C	2001
Neulasta®	Pegfilgrastim	GCSF[a]	20000	Neutropenia	2002
Somavert®	Pegvisomant	GH[b] antagonist	4–5 × 5000	Acromegaly	2003
Macugen®	Pegaptanib	Anti-VEGF[c] aptamer	40000	Age-related macular degeneration	2004

[a]GCSF, granulocyte-colony stimulating factor.
[b]GH, growth hormone.
[c]VEGF, vascular endothelial growth factor.
[d]SCID, severe combined immunodeficiency disease.
[e]ALL, acute lymphoblastic leukemia, acute lymphocytic leukemia.
[f]CML, chronic myeloid leukemia.18pt