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A New Approach to Drug Therapy: Fc-Fusion Technology

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Abstract

Fc-fusion proteins have been successfully implemented in the treatment of many diseases. Advances in engineering and design of these therapeutic proteins have helped prolong the drug half-life, which in turn allows for longer dosing intervals (i.e. weekly or bi-weekly administration) and, thus, may improve patient adherence in a real world setting. In this review, we provide a brief summary of half-life extension technologies. Here, we focus on IgG-Fc fusion and the key roles that the Fc fragment plays in both physiology and drug therapy, and the potential to elicit immune responses in humans. This review provides examples of various recombinant Fc-fusion protein drugs, including, etanercept (Enbrel®) for the treatment of various forms of arthritis, aflibercept (Eylea®), for the treatment of neovascular age-related macular degeneration and dulaglutide (Trulicity™) for the treatment of type 2 diabetes. All of these fusion proteins can be administered at least weekly. Overall, Fc-fusion proteins have proven to be a successful alternative to improve pharmacological properties of therapeutic drugs, with more convenient utilization in the real world and with low immunogenic potential.

Keywords: Fc-Fusion; Half-life extension; Fc fragment; Fusion protein technology

Introduction

There is evidence of the potential impact of less frequent dosages on quality of life and adherence to therapies for chronic diseases [1-3]. Therefore, improving the time a drug is available in circulation to exert its action is critical in pharmacotherapy. Recent advances in pharmacological engineering and design revealed the potential of fusion protein molecules to help prolonging intervals between doses. Among them, several fragment crystallizable (Fc)-fusion proteins have been successfully implemented in the treatment of various diseases, including autoimmune and inflammatory, cancer, infectious, cardiovascular and type 2 diabetes mellitus [4-8]. The current article intends to provide a brief review for clinicians on Fc-fusion protein technology.

Half-life extension technologies

Biologically active proteins and peptides play a significant role in clinical management of human disease. In fact, more than 180 therapeutic proteins and peptides have been approved by the FDA [9]. However, many of these peptides and proteins have less than ideal pharmacokinetic properties, either because they are eliminated by kidney filtration due to their small size and/or due to proteolytic metabolism, thus imposing constant infusions or frequent subcutaneous administration to keep their circulating concentrations within the effective range, which is clinically undesirable [9-16].

In principle, two main strategies are commonly used to reduce the impact of the aforementioned clearance mechanisms on the time-action of a peptide or protein of interest.

The first strategy is depot formulations, which provide an extended drug payout from the site of administration into the systemic circulation, using polymeric and lipid microparticulate systems, in-situ depot-forming systems and implants (refer to reviews [17-19]) that allow proteins and peptides ("the active drug") to be continuously released from the subcutaneous tissue for extended periods of time at sufficiently high concentrations to exert pharmacological activity. In general, therapeutic peptides or proteins in this approach require limited or no molecular engineering, as ideally the depot formulation protects against metabolism, and renal clearance is overcome by constantly releasing the peptide or protein into the circulation [17-19]. One example of an extended-release formulation of a small peptide is Exenatide extended-release (ER) (Bydureon®, Astra Zeneca, for type 2 diabetes mellitus) for once weekly subcutaneous administration. Exenatide ER is encapsulated in 60 µm diameter microspheres of poly-(D,L-lactide-co-glycolide) and is supplied as a dry powder with an aqueous diluent. Therefore, the injectable suspension is prepared by the patient just before use. This technique allows for a once a week administration, while exenatide by itself has a very short half-life and has to be administered twice a day (Byetta®, Astra Zeneca, for type 2 diabetes mellitus).

The second general approach consists of reducing renal filtration and elimination by increasing the size of the therapeutic peptide. This can be achieved by:

(a) Increasing the hydrodynamic radius of the therapeutic protein by chemical conjugation with a large polymer like methoxy polyethylene glycol (PEG) or, more recently, by recombinant techniques; or

(b) Increasing the molecular weight of the protein of interest to approximately 60 to 70 kilo Dalton (kDa), the renal threshold for renal filtration. This can be achieved by either non-covalent association of the therapeutic peptide to a larger carrier protein, such as circulating albumin or by covalent fusion of a therapeutic peptide to a carrier protein via genetic recombination [9,20-25].

In covalently fused proteins, the pharmacologically active moiety does not dissociate from the fusion partner, but works and interacts with the target as a large, fusion protein. The crystallizable fragment

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of a human immunoglobulin (IgG-Fc), albumin, or transferrin are commonly used as fusion partners. While fusion of a protein of interest with a carrier like albumin provides only half-life extension, fusion with an IgG-Fc can additionally achieve various therapeutic effects depending on the underlying disease [26-31].

Due to increased circulating half-life over the native peptide or protein, engineering the therapeutic moiety to provide stability against proteolytic metabolism might be necessary.

The effects of depot formulation and increasing the size of a therapeutic are not mutually exclusive, as a component of the depot effect (delayed absorption) is also realized by subcutaneous administration of a large molecule, which reaches the systemic circulation via the lymphatic system [16].

The Fc fragment in physiology

IgG represents approximately 85% of all immunoglobulins (IgA, D, E, G, M) in the serum and non-mucosal tissue [16] (Figure 1). Together with albumin, IgGs have the longest half-life among plasma proteins [32] (Table 1). Beyond reduced renal elimination due to large size, the IgG serum half-life may additionally be explained by the interaction with the *neonatal Fc receptor (FcRn)* in endothelial cells [33,34]. Binding to endothelial FcRn allows IgG, which is otherwise destined for endocytosis and further lysosomal degradation, to be recycled and released back into circulation [35] (Figure 2).

Additionally, IgG plays a critical role in the protective immunity against many pathogens and toxins by interacting with the cell surface *Fcγ receptor (FcγR)* on leukocytes, which mediate downstream effector mechanisms [30,36-38]. This process is known as cytotoxicity and is mediated through antibody-dependent cellular cytotoxicity (ADCC)

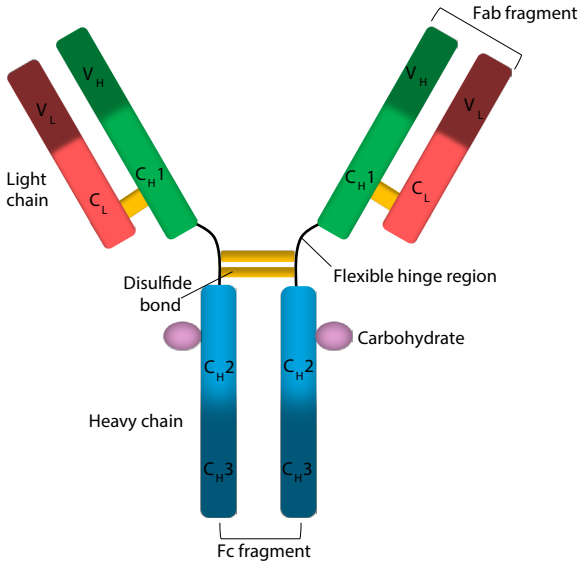

Figure 1: Structure of IgG antibody. Human IgG is made up of two identical heavy chains and two identical light chains. The two heavy chains are categorized into four subclasses (i.e., 1-4) and two variants make up the light chains (i.e., κ and λ), forming two antigen-binding fragment (Fab) arms that attach to the Fc fragment Figure 1. The unique property of the hinge structure (i.e., the region that links the Fc and Fab portions of the antibody molecule) plays a major role on the stability, flexibility and distances spanned by the two Fab arms and the Fc fragment [64-66]. Abbreviations: Fab=fragment, antigen-binding; Fc=fragment, crystallizable; C_L=constant domain, light chain; C_H=constant domain, heavy chain; V_L=variable domain, light chain; V_H=variable domain, heavy chain.

Ig Isotypes [16]	IgA	IgD	IgE	IgG	IgM
Serum concentration (mg/mL)	1.5-2.6	0.04	0.0003	9.5-12.5	0.7-1.7
Serum half-life (days)	6	3	2.5	23	5

This table provides a simplified comparison between each Ig isotype

Table 1: Characteristics of Ig Isotypes and IgG subclasses.

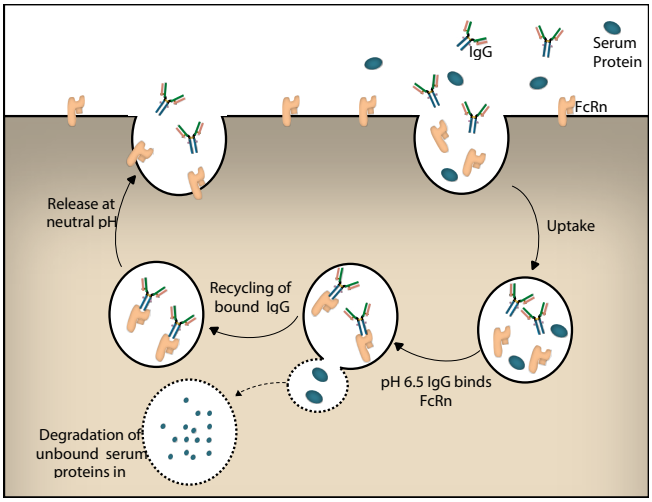

Figure 2: FcRn-mediated IgG recycling. FcRn-mediated IgG recycling plays an important role in extending plasma half-life of native IgG. IgG uptake into the cell, including endothelial cells, occurs via fluid phase pinocytosis with subsequent binding to FcRn in the acidified environment (~pH 6.5) of the endosomal compartment. IgGs are thought to be protected from degradation by recycling to the cell surface where the neutral pH facilitates dissociation from the FcRn and release back into circulation [67].

and complement-dependent cytotoxicity (CDC) and ultimately results in cell lysis, which is the basic protective response against pathogenic agents [5,39-41].

The Fc fragment in therapeutics

IgG is the most commonly used antibody class for therapy, with a molecular weight of approximately 150 kDa [16]. In Fc proteins, the peptide or protein of interest (a ligand, an extracellular domain of a soluble receptor, etc.) is fused with an Fc fragment primarily to benefit from half-life extension [13]. Taking advantage of size increase and the natural recycling process of IgG, Fc proteins are thought to be protected from degradation by recycling IgG FcRn fused proteins into circulation.

The choice of the IgG isotype is critical in therapeutics: IgG1, IgG2 and IgG4 are often preferred to IgG3 due to their longer half-lives of approximately three weeks [42-45]. Also, IgG subtypes differ on their ability to exert effector functions depending on the binding affinity of IgG to FcγRs: IgG1 and IgG3 have the highest binding affinity and, therefore, are more cytotoxic [46]. In contrast, the binding affinity of IgG4 is approximately 10-fold less than the affinity of IgG1 and IgG3, whereas the binding affinity of IgG2 is undetectable [47,48]. The choice of either one or other IgG isotype as an Fc fusion partner will depend of the desired level of half-life extension and cytotoxic activity purchased for the final compound. Most of the approved therapeutic antibodies are indicated for the treatment of cancer and autoimmune diseases. They belong to the IgG1 subclass because of its potent ability to exert effector functions through *high affinity* binding to the Fc receptors, which is an important advantage for the treatment of those diseases [42,49,50]. Inversely, the IgG2 and IgG4 subclasses are the preferred

backbone of a therapeutic candidate when a lack of cellular activity is desired [40].

Immunogenicity of protein therapeutics

Despite the fact that the protein-based biologics might be similar or identical in sequence to the native human protein, immunogenicity is a major safety concern during the development of any therapeutic protein. Protein-based biologics have the potential to elicit immune responses in humans. Immune responses to therapeutic proteins are characterized by the generation of anti-drug antibodies, which may neutralize its pharmacodynamics effect, affect the pharmacokinetic profile of the biologic, cross-react with its natural counterpart, or have no negative consequences at all [51]. Factors influencing immunogenicity of a therapeutic protein are many, and could range from extrinsic factors, such as aggregates and adjuvant-like contaminants and the patient's immunological status and co-medication, to intrinsic factors, such as the presence of B-cell or T-cell epitopes (the part of an antigen that is recognized by the immune system) on the therapeutic protein itself. Of particular concern are sequences generated at the junction of the active moiety and the carrier protein in fusion proteins, as these are generally novel to the human immune system. The potential for T-cell mediated immunogenicity in humans can be reduced by examining the sequence of fusion proteins for potential T-cell epitopes using *in silico* algorithms; subsequently, lack of immunogenicity needs to be confirmed by clinical data. The presence of anti-drug antibodies is not predictive of anaphylaxis or other hypersensitivity reactions from occurring [52,53].

Selected IgG-Fc fusion molecules in clinical use

To date, there are ten marketed Fc-fusion protein therapeutics that are approved by the FDA and EMA. We will describe three selected IgG-Fc fusion proteins in more detail below. For more information on other clinically used Fc-fusion therapeutics not described below, see reviews [9-16]. Etanercept (Enbrel®) was approved by the FDA in 1998 as a biweekly or weekly subcutaneous injection for the treatment of various forms of arthritis including rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis, as well as, plaque psoriasis and ankylosing spondylitis. Etanercept is a human tumor necrosis factor (TNF) receptor p75 Fc fusion protein and is the first successful example of using a soluble receptor-Fc fusion protein as a therapeutic drug and the only TNF-blocker commercially available in a fusion protein [54]. Etanercept is the result from the fusion of the 75 kDa soluble extracellular ligand-binding domain of the TNF-α receptor II (TNFR II) to the Fc domain of human IgG1 (Figure 3A). The Fc fragment prolongs the half-life of the compound, resulting in an extended and more profound biologic effect than its native form [54]. In addition, etanercept has less immunogenic potential compared to anti-TNF monoclonal antibodies [55]. The mechanism of action of etanercept is through the neutralization of both the membrane-bound and soluble forms of TNF-α, preventing TNF-mediated cellular responses and therefore modulating the concentrations of serum inflammatory cytokines, serum matrix metalloproteases, and adhesion molecules. Etanercept is considered safe and effective in both adults and children [55]. Antibodies to the TNF receptor portion or other protein components of the etanercept drug product were detected in approximately 6% of patients with adult rheumatoid arthritis, psoriatic arthritis, active ankylosing spondylitis or severe plaque psoriasis. These antibodies were all non-neutralizing. Treatment effects from juvenile patients with polyarticular idiopathic arthritis were similar to those seen in adult patients with rheumatoid arthritis. Commonly reported adverse events associated with etanercept include injection site reactions and infections, such as upper respiratory tract infection, sinusitis and influenza. Similar to other TNF blockers, there is an increased risk of more serious infections including, but not limited to, tuberculosis and bacterial sepsis [55]. However, TNF-α is a central regulator of inflammation, particularly in normal immune responses to certain pathogens. The increased risk in opportunistic infections observed in patients treated with anti-TNF-α therapy is explained by the immunomodulatory effects related to the blocking of TNF-α and the underlying disease and not related to the Fc component of the fusion protein [56,57].

Another example is the recombinant Fc fusion protein, aflibercept (Eylea®; Regeneron, Terrytown, NY, USA), approved in 2011 and administered every 4 to 8 weeks by intravitreal injection for the treatment of neovascular (i.e. wet) age-related macular degeneration (AMD) [58]. AMD is characterized by the growth of abnormal blood vessels in the eye (i.e., choroidal neovascularization) stimulated by angiogenic factors belonging to the VEGF family [59]. Aflibercept is a recombinant fusion protein associating portions of human VEGF receptors extracellular domains fused to the Fc portion of human IgG1 (Figure 3B) [58]. It has been specifically designed for high affinity to its ligands and for minimal interactions to the extracellular matrix, leading to an enhanced pharmacokinetic profile [60]. Aflibercept binds to the angiogenic factors thereby inhibiting the binding and activation of native VEGF receptors. Overall, the incidence of anti-drug antibodies following treatment with aflibercept remained low, ranging from 1% to 3% of patients across the neovascular age-related macular degeneration, retinal vein occlusion and diabetic macular edema studies and there were no differences in efficacy or safety between patients with or

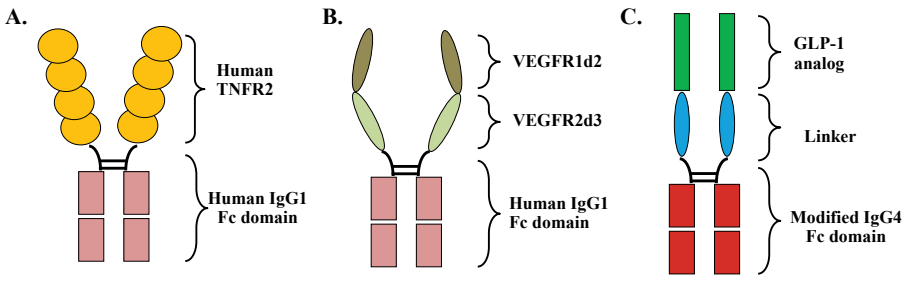

Figure 3: Simplified diagram of the molecular structures of etanercept, aflibercept and dulaglutide. A. The molecular structure of etanercept is the result from the fusion of the extracellular ligand-binding domain of TNFR II to the Fc domain of human IgG1 [54] (data from Wallis 2008 [68]). B. The molecular structure of aflibercept consists of portions of human VEGF receptors extracellular domains that link to the Fc domain of human IgG1 [58] (data from Platania et al. 2015 [69]). C. The molecular structure of dulaglutide consists of a GLP-1 analog fused to the Fc domain of a modified IgG4 [4] (data from Kuritzky et al. 2014 [68]). Black bars represent disulfide bridges. Abbreviations: VEGFR1d2=domain 2 of vascular endothelial growth factor receptor VEGFR1; VEGFR2d3=domain 3 of vascular endothelial growth factor receptor VEGFR2

without immunoreactivity. Other common adverse reactions reported in patients treated with aflibercept included conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure [58].

Finally, glucagon-like peptide-1 receptor agonist, dulaglutide (Trulicity™, Eli Lilly and Company, Indianapolis, IN), was approved in 2014 as a once weekly subcutaneous injection to improve glycemic control in adults with type 2 diabetes [61]. The molecule is a recombinant fusion of glucagon-like peptide-1 (GLP-1) analog consisting of two identical disulfide-linked chains covalently linked to a modified IgG4 heavy chain-Fc fragment, which are fused together by a small peptide linker (Figure 3C) [4]. The GLP-1 analog portion of dulaglutide contains 3 mutations compared to the native GLP-1 peptide. The alanine change at position 8 to glycine confers resistance to inactivation by the enzyme dipeptidyl peptidase-IV and the glycine change at position 22 to glutamic acid increases solubility of dulaglutide. The arginine change at position 36 at the junction between the GLP-1 moiety and the linker sequence to glycine de-immunizes the fusion protein. The IgG4 Fc region of dulaglutide was optimized to reduce interaction with Fcγ receptor I and to eliminate half-antibody formation [4]. In addition, the C-terminal lysine was removed from the IgG-Fc. In the clinical program, 1.6% of dulaglutide-treated patients developed anti-drug antibodies with no differences in efficacy or safety between patients with or without antibodies. Similar to other drugs in the GLP-1 receptor agonist class, common adverse events related to dulaglutide are gastrointestinal in nature, including nausea, vomiting and diarrhea. These effects are generally mild to moderate in severity and transient [61].

IgG-Fc fusion therapeutics in a real world setting

The main reason why this technology was developed was to enable therapy with short-acting proteins. The extension of a molecule's half-life offers additional benefits for patients. IgG-Fc fusion therapeutics, by extending the half-life of the drug, may provide clinically relevant advantages regarding patient preference and adherence. In general, patients suffering from chronic diseases are more likely to adhere to medications that require less frequent, intermittent dosing regimens. Studies have demonstrated an inverse relationship between medication adherence and dosing frequency in patients with chronic diseases. Up to a 19% decrease in taking adherence, up to a 23% decrease in regimen adherence, and up to a 54% decrease in timing adherence in chronically ill patients whose treatment required them to take multiple daily doses compared to patients who are on once-daily regimens [62]. Similarly, researchers found that adherence was up to 12% higher in patients on a once-weekly dosing regimen compared to patients on more frequently dosed agents for the same conditions and up to 96% of patients preferred an intermittent dosing regimen [63]. Therefore, a more favorable dosing regimen may enhance patient adherence and ultimately the patient's health.

Concluding statements

In conclusion, Fc-fusion proteins have proven to be a successful alternative to improve pharmacological properties of therapeutic drugs with low immunogenic potential. Overall, these drugs have an acceptable safety profile with adverse events that are generally specific to the mechanisms of action of each drug class. By utilizing and manipulating Fc-Fc receptor interaction, developers are able to improve pharmacokinetics, significantly increase serum half-life and selectively enhance or disable effector functions, all while maintaining drug efficacy. Combined with an increased knowledge of the complexity of antibody disposition, Fc-fusion has become an ideal platform for increasing half-life, thus reducing dosing frequency, reducing immunogenicity by providing optimal effects while avoiding undesired complications. Overall, advances in Fc-fusion technology have led to greater flexibility when developing therapeutics by selectively addressing the needs of various disease settings.

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