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Narrative Review

Anti-TNFα Biologics in the Pharmacotherapy of Rheumatoid Arthritis: Effectiveness and Safety of Infliximab, Adalimumab and Etanercept

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology. Traditionally, pharmacotherapy of RA involved non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). However, focus now has been diverted to biologic DMARDs. Tumor necrosis factor alpha (TNFα) plays pleiotropic roles in RA pathogenesis. Hence, anti-TNF biologics offer attractive therapeutic utility. Literature contains numerous studies comparing either the effectiveness or the safety of the three drugs of interest; infliximab, adalimumab and etanercept, in terms of; patient response to treatment in a cohort and in vitro properties of the drugs. Concern at the absence of a review that comprehensively exploits both the effectiveness and safety, this review aims towards not only presenting the observed discrepancies, but also discussing the causes for them and providing experimental results from studies obtained via an extensive literature survey. Critical analysis of the effectiveness and safety profiles of licensed anti-TNF agents; infliximab, adalimumab and etanercept revealed that, a single drug cannot be named as the most efficacious. Nevertheless, anti-TNF therapy associates challenges of systemic toxicity, heterogenous patient response and partial remission. Advancement in research aiming at alleviating the existing drawbacks of anti-TNF therapy is essential.

Keywords: Rheumatoid arthritis, Anti-TNF therapy, Pharmacotherapy

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Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease of unknown etiology. It characteristically presents with joint inflammation that leads to joint damage, loss of function and ultimately disability.[1-3] Moreover, RA affects approximately 1% of the global adult population, occurring in 20–50 cases per 100 000 annually,[4,5] incidence being two to three times common in women than in men.[6,7]

Nevertheless, though RA primarily occurs in the joints, it involves extra articular manifestations and systemic comorbidities. Substantial individual and socioeconomic burden resulting from musculoskeletal defects, reduced quality of life, declined work capacity and increased medical costs remain serious concerns.[8-10]

Furthermore, though recent advances have contributed positively to its course, RA continues to present challenges to modern medicine. The discovery of tumor necrosis factor *alpha* (TNFα) as the central dogma in the pathogenesis of RA[11,12] resulted in broad consensus that anti-TNF biologics will be an effective treatment approach. Subsequently, anti-TNF biologic therapy did show significant improvements in the quality of life in majority of RA patients.[13,14] However, the concerns arose when an estimated 30%–40% of patients remained unresponsive to treatment while very few enjoyed complete remission.[15,16] Moreover, association of biologics with increased risk of adverse effects suggested the necessity of reviewing the effectiveness and safety of existing therapeutics.[17,18] Thus, this review exploits the comparison of effectiveness and safety of three prominent anti-TNFα biologics, infliximab, adalimumab and etanercept, aspiring to provide platform and background for the development of more effective and safer therapeutics.

Pharmacotherapy

According to the treatment guidelines published by the American College of Rheumatology,[19] goals of RA pharmacotherapy are; reduction of disease activity, establish remission, tight control through medical management and prevention of further joint damage. However, Alam et al[20] and Murphy et al[21] address improvement of the quality of life as another prominent goal.

Traditionally, RA has been treated with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs). The NSAIDs and glucocorticoids remain first line drugs, whereas DMARDs are second line drugs.[22,23]

DMARDs are defined as medications that reduce or halt the disease progression by rapid and sustained suppression of inflammation, but incapable of curing the disease.[24] They can be categorized as, conventional DMARDs (cDMARDs) and newly introduced biologic DMARDs (biologics). Among cDMARDs, the most efficacious is methotrexate (MTX),[25] due to its highest retention rates. Nevertheless, combination of MTX with one or more of the other cDMARDs or combination of MTX with a biologic has shown improved response in clinical trials than monotherapies of DMARDs.[26,27]

Biologics

Biologics are drugs produced from living organisms or contain components of living organisms (blood, blood components, cells, allergens, genes, tissues and recombinant proteins),[28] that have been formulated to specifically block or alter the function of cytokines.

Anti-TNFα Biologics

Placing TNFα at the center of RA pathogenesis has led RA to be the first disease for which anti-TNF biologics were used.[28] In clinical settings, anti-TNF biologics have been efficacious in 60%–70% of RA patients whose disease activity was persistent despite cDMARD treatment.[29] Apart from improving the clinical symptoms of RA, TNF antagonists provide protection against joint destruction, disability and improve quality of life,[30] thus addressing most of the aims of RA pharmacotherapy.

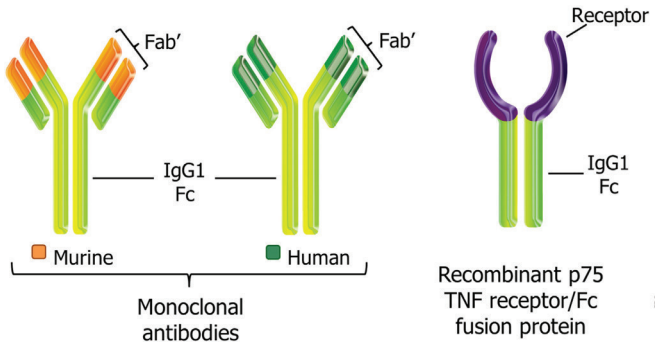

Figure 1. Schematic Illustration of Molecular Structures of Anti-TNFα Biologics (from left to right; infliximab, adalimumab and etanercept).[32]

Currently, three anti-TNF biologics; infliximab, adalimumab and etanercept approved by the Food and Drug Administration (FDA) are utilized in clinical settings.[31]

Considering the structures of these drugs (Figure 1), infliximab is a chimeric monoclonal antibody that has been genetically engineered by the fusion of two murine TNF-binding epitopes and a Fc portion of a human IgG1. Conversely, adalimumab is a human monoclonal antibody engineered by the combination of two human TNF-binding epitopes and a Fc portion of a human IgG1. Moreover, etanercept is the combination of two naturally occurring soluble human TNF receptors and a Fc portion of a human IgG1.

Furthermore, anti-TNF biologics currently in phase III trials; golimumab, a human monoclonal antibody;[33] and certolizumab pegol, a pegylated fab' fragment of a humanized monoclonal antibody against TNF,[34] are expected to yield similar results as the licensed agents.

Comparison of Effectiveness

Comparison of Clinical Properties

Clinical efficacy of infliximab, adalimumab and etanercept in RA is achieved by their inhibitory properties on; cell activation, cell proliferation, cytokine and chemokine production, inflammation, immune regulation, angiogenesis, and extracellular matrix degradation.[30] Thus, comparison of the clinical properties (Table 1) of anti-TNF biologics is essential to review their effectiveness.

According to Kaymakcalan et al,[35] measurements on binding affinities, using BIAcore and radioimmunoassay methods, reported higher values for sTNFα than mTNFα. on the contrary, Sakorafas et al[36] reported equal affinities for both sTNFα and mTNFα, when kinetic exclusion assay was employed for the measurements, suggesting that the discrepancy in findings may be a consequence of utility of different assays. Moreover, Kaymakcalan et al[35] suggested that, this inconsistency may be due to structural variations (Figure 2). However, it is yet unknown whether the binding affinities of these drugs play an important role in different clinical outcomes.[49]

Considering CDC, both infliximab and adalimumab show higher effectiveness, whereas etanercept remain less effective. CDC involves binding of C1q to CH2 domain of IgG1, which

Table 1. Comparison of Clinical Properties of Infliximab, Adalimumab and Etanercept

Property		Infliximab	Adalimumab	Etanercept	Reference(s)
Binding	sTNFα	+++	+++	+++	35
	mTNFα	++	++	++	35
		+++	+++	+++	36
Functional properties shown on mTNFα expressing cells	CDC	+++	+++	+	37, 38, 39
	ADCC	+++	+++	+++	38
		+++	+++	+	37, 39
	Reverse- signaling	+++	+++	-	38
Downregulation of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-18, GM-CSF)		+++	+++	+++	40,41,42
Upregulation of anti-inflammatory cytokines (IL-4, IL-10, IL-12)		+++	+++	-	43,44, 45
Improving T_{reg} and Suppressing T_{eff}		+++	+++	-	46
Induction of apoptosis		+++	+++	-	38, 44, 47, 48

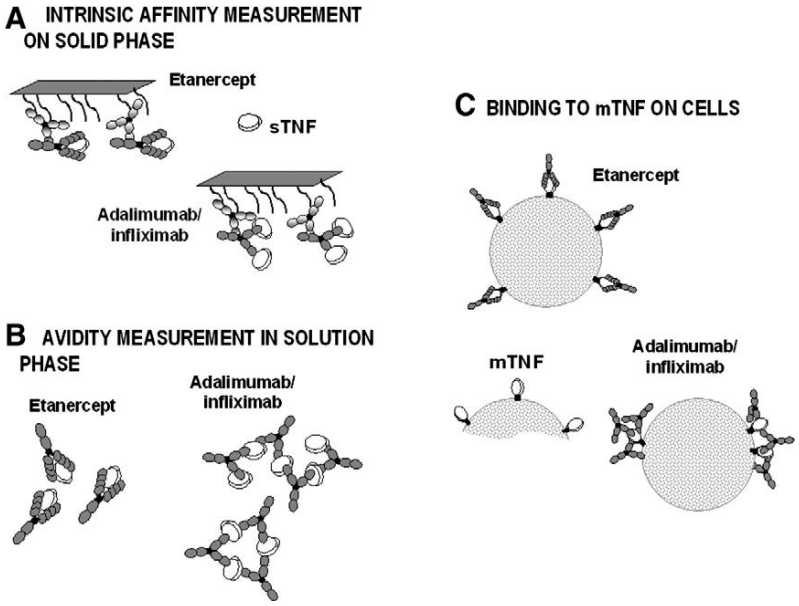

Figure 2. Illustration of Binding Interactions Between Anti-TNFα Agents (Black) and TNFα, as Captured by Biosensor Chips Covalently Attached to Polyclonal Goat Anti-human IgG Fc. Reprinted with permission from Kaymakcalan et al.[35]

initiates the classical complement cascade, thus leading to the eventual formation of membrane attack complex and the resultant cell lysis.[39] Therefore, this discrepancy is believed to be a result of the structure-influenced binding abilities of TNF antagonists to the first complement component, C1q. Accordingly, Arora et al[37] evaluated binding abilities of the three drugs to C1q, using radiolabeled ^{125}I bound to immobilized C1q (Figure 3). Both infliximab and adalimumab showed significant increase in binding along with the increment of C1q concentration, whereas etanercept reported only a slight increase.

Moreover, infliximab, adalimumab and etanercept commonly possess the Fc portion of IgG1 (Figure 4), whose CH2 domain activates C1q. However, etanercept does not carry the CH1 domain and hinge region of IgG1.[50] This results in conformational hindrance for the proper binding with C1q, thus making its potency low. Nevertheless, CH1 domain being the platform for activation of complement component C3,[51] and hinge region being necessary for the formation of membrane attack complex[52] further explain the reduced CDC activity by etanercept.

As for ADCC, all three drugs showed similar activity, when mTNF-transfected Jurkat T cells were used as target,[38] whereas infliximab and adalimumab were efficacious than etanercept in NS0 cells[39] and CHO cells.[37] Therefore, this discrepancy in etanercept-induced ADCC may be perceived as a consequence of the difference in the species of target cell used. However, structurally all three drugs possess both CH2 and CH3 domains of the Fc region of IgG1 (Figure 4), which are crucial for the anti-TNF agents to bind with Fc receptors of NK cells.[53] The NK cells in turn lyse of the target cells by granzyme B and perforin. Consequently, all three drugs should show equal ADCC activity, theoretically.

Reverse signaling, a function of TNF agonists for the inhibition of TNFα-producing cells, is mediated by pathways independent of CDC and ADCC (Figure 5). However, upon binding to mTNFα-expressing Jurkat T cells, both infliximab and adalimumab, induce apoptosis and cell cycle G0/G1 arrest, whereas etanercept did not. Watts et al[55] reveal that, this inability of etanercept may be due to the absence of complementary residues to bind with serine residues of mTNFα in order to initiate apoptotic signaling.

As for downregulation of pro-inflammatory cytokines, all three agents have been equally efficacious. According to

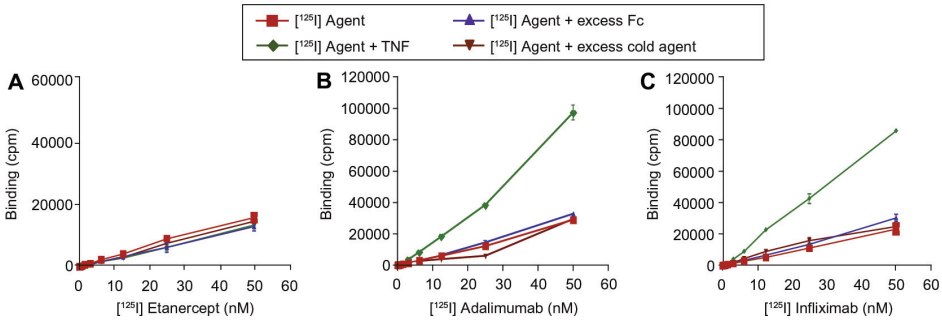

Figure 3. Binding abilities of anti-TNF agents (A) etanercept, (B) adalimumab and (C) infliximab to C1q, evaluated by radiolabeled ^{125}I bound to immobilized C1q. Reprinted with permission from Arora et al.[37]

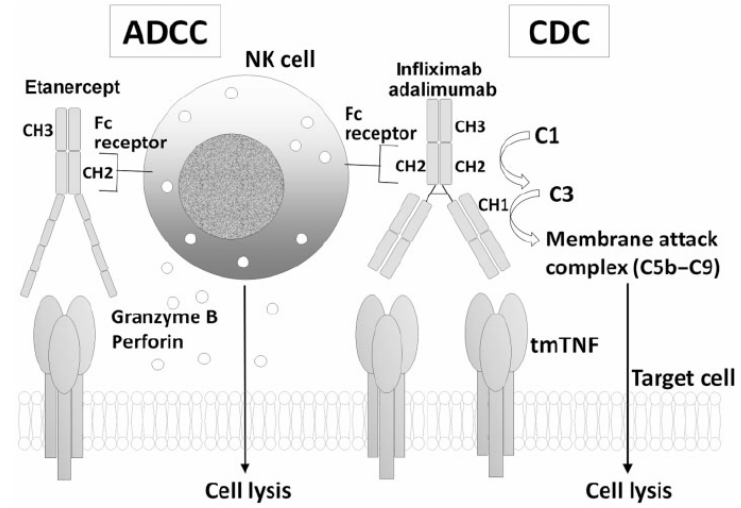

Figure 4. Structures of Infliximab, Adalimumab and Etanercept With Domains Relevant to CDC and ADCC Activity.[54]

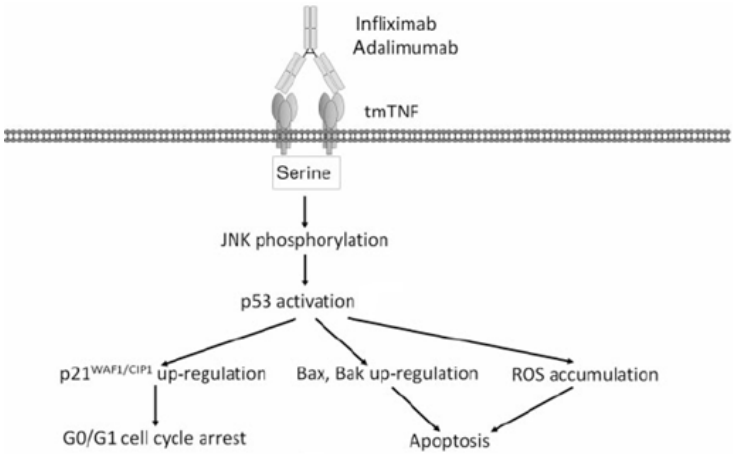

Figure 5. Mechanism of Reverse Signaling by Infliximab and Adalimumab.[54]

Ohshima et al,[45] elevated serum IL-6 levels rapidly diminished in each set of patients who received one of the three agents. Nevertheless, etanercept downregulated IFN-γ, GM-CSF and IL-18[42] production *in vitro* as efficiently as infliximab and adalimumab.

However, infliximab and adalimumab have successfully augmented anti-inflammatory cytokine levels *in vitro*, whereas etanercept has failed to do so. According to Mitoma et al[43] and Horiuchi et al,[54] all three agents stimulated mTNFα-expressing Jurkat T cells, whereas only infliximab and adalimumab upregulated IL-10 levels *in vitro*. Nevertheless, elevated serum IL-10 levels in RA patients were further augmented in patients treated with infliximab and adalimumab, whereas no change was observed in patients who were given etanercept.[45]

Considering induction of apoptosis, both the monoclonal antibody drugs have been efficacious, whereas the receptor protein has been ineffective. Infliximab and adalimumab have induced apoptosis in cells which express mTNFα such as; lamina propria T-lymphocytes,[48] monocytes,[44] and macrophages.[40] Conversely, they have failed to induce apoptosis in cells which do not express mTNFα, such as lymphocytes.[47] Therefore, induction of apoptosis by infliximab and adalimumab, can be understood as a process dependent on reverse-signaling; a functional property shown only on mTNFα-expressing cells. Thus, the inability of etanercept to induce apoptosis can be understood as a consequence of its ineffectiveness in reverse signaling.

Moreover, improvement of T_{reg} and suppression of T_{eff} by infliximab and adalimumab, is believed to be the result of their influence on the viability T_{reg} and T_{eff},[56] through mechanisms such as induction of apoptosis. Consequently, etanercept fails to regulate the activity of T cells[55] as it is inefficacious in inducing apoptosis.

Comparison of Patient Response to Treatment

Effectiveness can be further assessed by reviewing the patient response to treatment (Table 2). Regardless when given as monotherapy or in combination with MTX, etanercept has shown augmented response in clinical trials. Nevertheless, it has reported high retention rates as both first- and second-line biologics. Furthermore, literature considers etanercept as the drug of choice for short term therapy. Therefore, collectively, etanercept shows highest rates in overall patient response to therapy. Furthermore, adalimumab can be considered the

Table 2. Comparison of Patient Response to Treatment in Infliximab, Adalimumab and Etanercept Therapy

Criterion	Infliximab	Adalimumab	Etanercept	Reference(s)
Drug monotherapy vs. MTX monotherapy	++	+	+++	57-59
Drug + MTX combination therapy	+	++	+++	60-65
Short term therapy (<1 year)	+	+++	+++	66
Long term therapy (>1 year)	+	+++	++	66
Disease remission	+	+++	++	67
Retention rate as 1st line biologic	++	++	+++	68
Retention rate as 2nd line biologic	++	++	+++	68

second most efficacious drug in patients due to highest rate of disease remission and being the drug of choice in long term therapy. Nevertheless, infliximab appears to be the least efficacious in terms of treatment response.

Contraindications

As any other therapeutic method, anti-TNFα biologic therapy too has its contraindications (Table 3), which pose a challenge to its therapeutic role.

Table 3. Side Effects Associated With Anti-TNFα Biologic Therapy

Serious Adverse Events	Infections	Infusion Reactions
MI and congestive heart failure	Reactivation of TB	Pruritus
Lymphoma	Histoplasmosis	Rash
NMSC	Listeriosis	Dyspnea
Demyelination	Candidiasis	Hypertension
Hematological effects	Aspergillosis	Chest discomfort
LFT abnormalities	Pneumocystis pneumonia	Nausea

Abbreviations: TB, tuberculosis; MI, myocardial infarction; NMSC, non-melanoma skin cancer; LFT, liver function tests.
Adapted from Dogra and Khullar.[69]

Initially, anti-TNFα biologics were found to reduce the risk of cardiac diseases.[70] However, along with the reported increment of total cholesterol and low-density lipoprotein levels subsequent to anti-TNFα therapy,[71] they are considered to impose risk for MI and congestive heart failure.

Reportedly, TNFα regulates the cytokine mediated cancer immunosurveillance, and Ramanarayanan et al[72] suggest that, blockage of TNFα may revoke anti-tumor immunity and increase the risk of malignancies. Based on more extensive data, current FDA guidelines report an augmented risk of lymphoma in TNF antagonist treated subjects.[73]

Moreover, TNF antagonists reportedly destroy macrophagic granulomas containing *Mycobacterium tuberculosis*[74] via the induction of apoptosis. Therefore, treatment with anti-TNF agents associate high risk of reactivation of TB. Nevertheless, similar mechanisms have been related to the occurrence of other opportunistic infections.[75]

In the case of monoclonal antibody drugs, formation of anti-infliximab and anti-adalimumab antibodies[76] cause secondary inefficacy and may cause complete unresponsiveness eventually. Nevertheless, the presence of such antibodies may explain the increased infusion reactions reported with infliximab and adalimumab therapy.[77,78]

Comparison of safety

Numerous study groups have attempted to evaluate and compare the safety of infliximab, adalimumab and etanercept (Table 4). According to majority of literature, infliximab is the least safe as it is associated with the highest percentage of serious adverse events and infections. However, infliximab reports the least percentage of infusion reactions. Moreover, due to no serious adverse effects being reported at all, literature considers it the safest among the three. Etanercept reports a considerable percentage of infections. However, studies suggest that the increased infusion reactions caused by etanercept do not affect it being the safest, as infusion reactions can be easily dealt by applying cool pack (4°C), application of topical corticosteroids or by rotating the injection site.[79] As for adalimumab, it reports intermediate safety profile as it is associated with a considerable percentage

Table 4. Comparison of Safety of Infliximab, Adalimumab and Etanercept

Drug	Study Group/Year	Reference	Study Population		Adverse Effects (%)		
			Country	Number	Serious Adverse Events	Infections	Infusion Reactions
Infliximab	Lipsky et al, 2000	80	UK	67	85.1	87.5	-
Infliximab	St.Clair et al, 2004	65	USA	749	13.7	27.2	0.5
Infliximab	Westhovens et al, 2006 (START study)	81	USA	512	10.7	16.4	-
Etanercept	Weinblatt et al, 1999	82	UK	89	-	57.3	47.2
Etanercept	Bathon et al, 2000	83	UK	415	-	12.0	33.7
Etanercept	Van der Heijde et al, 2006 (TEMPO study)	63	USA	223	-	6.2	20.6
Adalimumab	Weinblatt et al, 2003 (ARMADA trial)	84	USA	140	-	6.4	24.2
Adalimumab	Van de Putte et al, 2004	85	Europe, Canada and Australia	434	-	18.6	10.6
Adalimumab	Keystone et al, 2004	86	USA and Canada	419	4.7	11.4	24.1
Adalimumab	Breedveld et al, 2005 (PREMIER study)	87	Australia, Europe and North America	799	39.6	3.6	-

of adverse effects, but less than that of infliximab and greater than that of etanercept.

Moreover, Table 5 further suggests etanercept as the safest and infliximab, the least safe among the three anti TNF agents.

Future Insight

Despite the clinical efficacy of anti-TNF agents, prevalence of potential drawbacks has led research to focus on finding solutions to alleviate negativities. A major drawback is failure to produce response in some patients or producing only a partial response. Nevertheless, molecular remission and the capacity to re-establish immunological tolerance remain elusive till date. Apart from that, systemic toxicity and complications of anti-TNF therapy remain a major challenge. Moreover, there is a notable absence of reliable predictive biomarkers to monitor therapeutic response and toxicity.

Ferrari et al[91] suggest the recruitment of novel strategies; 'Trojan Horse' and 'Guided Missile' drug delivery systems, to actively target and deliver anti-TNFα agents to target sites. Trojan horse drug delivery combines the two theories of polymer conjugation and nanoparticulate drug delivery (Figure 6), whereas guided missile drug delivery addresses formulating drugs as antibody conjugates and bispecific antibodies (Figure 7). Therefore, formulation of anti-TNF biologics according to these drug delivery concepts is believed to confer improved pharmacokinetic properties, promote in situ action and decrease systemic toxicity.

Nevertheless, researchers believe that gene array analysis will help define individual response to treatment, thus alleviate the heterogenicity in patient response.[93]

Conclusion

In conclusion of the review, it is evident that in terms of effectiveness related to clinical properties, both the monoclonal antibody drugs are efficacious than the receptor protein. However, considering patient response to treatment, both adalimumab and etanercept were superior to infliximab. Considering safety, etanercept is the safest whereas infliximab, is the least safe. Thus, a single drug cannot be named as the most efficacious in terms of both effectiveness and safety. Furthermore, systemic toxicity of anti-TNF agents, induction of heterogenous responses in patients, and above all, inability to achieve disease remission remain as challenges of current anti-TNF therapy.

Therefore, the improvement in structures and pharmacokinetic properties of anti-TNF agents may alleviate the reported drawbacks. Furthermore, it may lead to successful treatment of symptoms, improve safety profiles, and reduce

Table 5. Comparison of Safety of Infliximab, Adalimumab and Etanercept

Criterion	Infliximab	Adalimumab	Etanercept	Reference(s)
Drug survival rate	++	+	+++	57
Risk of infection	+++	++	+	88, 89
Discontinuation due to adverse effects	+++	++	+	63, 81, 83, 85, 87, 90

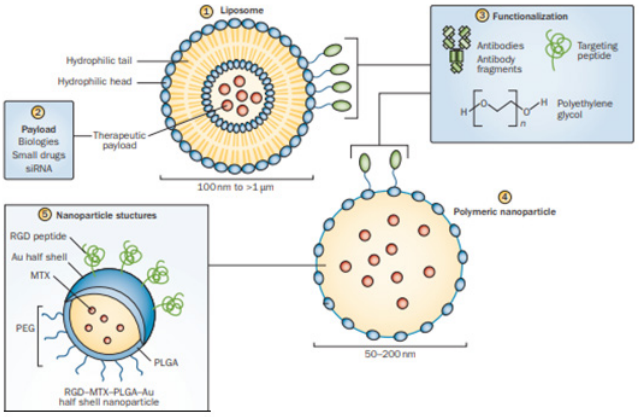

Figure 6. 'TROJAN HORSE' APPROACHES for Drug Delivery. Liposomes can be engineered to bind drugs and degrade only upon reaching the target site, thus it is believed to limit systemic toxicity. Moreover, nanoparticles can be conjugated to polymers that contain encapsulated drugs, thus promote target-specific delivery. Trojan horse drug delivery suggests formulation of drugs as polymeric nanoparticles by combining the above two theories, to achieve combined efficacy. An example is [5] conjugation of RGD to a methotrexate-loaded PLGA–Au nanoparticle32 providing active targeting of αVβ3-expressing endothelial cells. **Abbreviations**: PLGA, poly(lactic-co-glycolic) acid; RGD, Arg–Gly–Asp peptide; siRNA, small interfering RNA.[91]

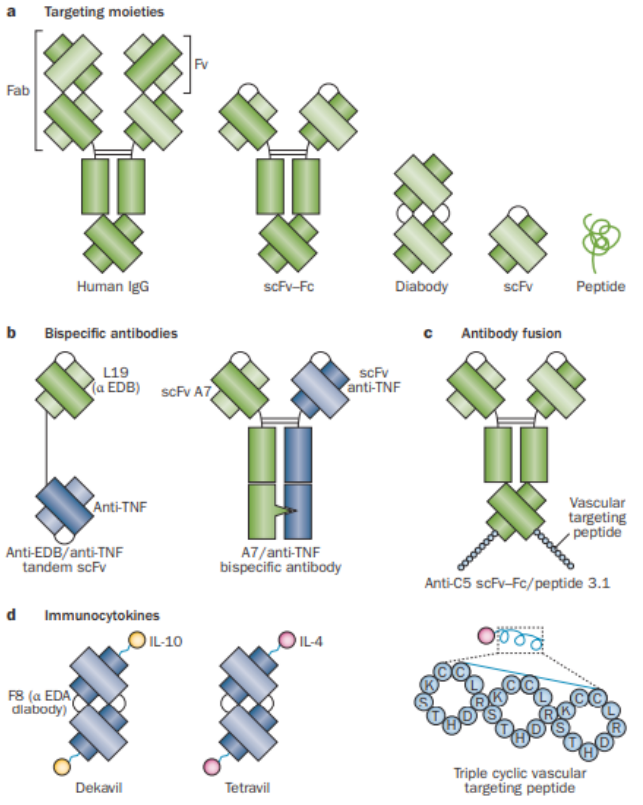

Figure 7. 'Guided Missile' Approaches for Drug Delivery. Formulating (a) drugs as antibodies, antibody derivatives and targeting peptides (b) drugs by the fusion targeting domain of bispecific antibodies to an anti-TNF drug (c) drugs by fusion of two antibodies (d) immunocytokines that target antibody derivatives as drugs, to promote target-specific drug delivery and reduce systemic activation. **Abbreviations**: EDA, extra domain A of fibronectin; EDB, extra domain B of fibronectin; scFv, single-chain variable fragment.[92]

burden for national healthcare systems.

Finally, though proposed future advances in therapy may improve effectiveness and safety, they however seem incapable of providing complete remission. Thus, advancement in research which aims at achieving a cure should be encouraged.

Authors' Contributions

ZB, conceived of the concept of the presented review, wrote the manuscript and revised it critically for important intellectual content.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

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