Anti-drug antibodies

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Abstract

Biological pharmaceuticals are increasingly used in modern medicine and give remarkable improvements for many different patient groups. Unfortunately, for several of these compounds, undesirable immune reactions are induced against the drug. The resulting anti-drug antibodies modify the pharmacokinetic and pharmacodynamic properties of the drug and, by blocking the drug-target interaction, reduce the effects of the treatment. Anti-drug antibodies may also increase the risk of hypersensitivity reactions by the formation of immune complexes. Furthermore, by cross-reacting with the endogenous homolog of the drug, the anti-drug antibodies might impair important physiological functions even after treatment cessation. As a consequence, anti-drug antibodies need to be taken in account when estimating the benefit-burden ratio of a treatment for an individual patient, but also when calculating the value of therapeutics on a socioeconomic level. In this review we give an overview over the current understanding of the immunogenicity against drugs, exemplified for patients with hemophilia A, multiple sclerosis, rheumatoid arthritis and Crohn’s disease. We discuss known and potential risk factors for anti-drug antibody formation and finally outline suggested strategies for prediction and prevention.

Introduction

The successful identification of important molecular interactions contributing to disease pathogenesis have led to the promising development of several biological pharmaceuticals (BPs), of which many have shown to be highly efficient treatments in clinical trials as well as in the post-marketing settings. These compounds can be designed to supplement missing factors [e.g. factor VIII for hemophilia A (HA)], to interfere with pathological processes by immunomodulation [e.g. interferon beta (IFNβ) for multiple sclerosis (MS)] or by blocking pathogenic signaling [e.g. anti-tumor necrosis factor alpha (TNFα) therapeutics for rheumatoid arthritis (RA) or Crohn’s disease (CD) and the anti-integrin therapy in MS or CD]. The quite specific mode of action of several BPs is promising, as physiological functions are mainly preserved, but pathological processes successfully targeted or replaced. However, the chronic nature of many of these diseases will require repetitive parenteral administration for life. This results in the risk of undesirable immune responses against the drug, leading to the formation of anti-drug antibodies (ADA). One major concern for clinicians is the loss of response (LOR) to the treatment due to the formation of ADA. The LOR can be due to two non-exclusive mechanisms. First, all ADA that bind to the BP, also referred to as binding antibodies (BAb), can alter pharmacokinetic properties of the agent by forming immune complexes with the drug. These immune complexes can enhance the clearance of the drug from the circulation, and thus potentially the effective dosage of the treatment. Second, so-called neutralizing antibodies (NAbs), which is essentially higher affinity BAbs, can directly interfere with the biological activity of the drug by binding to epitopes that lie within the active site or by steric hindrances of sites in close proximity to it. An additional concern with ADA-formation is the increase of adverse effects, which is negatively impacting the benefit-risk ratio of a therapy. For example, immune complexes of ADAs with BPs have been associated with an increased risk of type III hypersensitivity reactions. Furthermore, when a biological therapeutic supplements an endogenous homolog, ADAs against the pharmaceutical could potentially also target the endogenous homolog, with unforeseeable consequences for physiological functions even long after treatment cessation. An illustration of this potential complication is the case reports of severe thrombocytopoenia or pure red cell aplasia induced by anti-thrombopoietin or anti-erythropoietin NAbs that cross-react with the corresponding endogenous protein. Thus, the risk of ADA-formation needs to be taken in account when estimating the benefit-burden ratio of a treatment for an individual patient, and when calculating the value of a therapeutic on a socioeconomic level, but preferentially already during drug development.

In this review we discuss the immunological mechanisms involved in ADA-formation, the current methods used to detect ADAs, and outline a perspective to predict, prevent and deplete ADAs. In each section we provide examples from three different clinical fields: first, the treatment of HA with more than 50 years of experience with so called factor VIII inhibitors; second, the treatment of MS where the detection of ADAs were noted already within in the first pivotal trials for disease modifying BPs; and third, the treatment of RA and CD as examples from a field where the clinical relevance of ADAs is controversial, partly due to a lack of standardized methods to assess immunogenicity.

Immunological mechanisms involved in anti-drug antibody-formation

The frequencies of ADA positivity differ largely for different treatments and this is partly explained by the degree of immunological tolerance that exists naturally. For BPs with high bio-similarity to proteins encoded in the human genome, it would be expected that the immune system should tolerate the BP equally well as the corresponding self-proteins. Tolerance to a BP is regulated by central and peripheral immunological mechanisms and is dependent on the formation and activation of BP specific T- and B-cell clones and deletion of self-reactive clones. In the thymus the central tolerance eliminates immature T cells expressing T-cell receptors that form high-avidity interactions with self-peptides presented in the context of human leukocyte antigen (HLA). This T-cell maturation step will ensure that most self-reactive T-cell clones are deleted.

In patients with HA there is most likely low or non-existing tolerance to factor VIII, since the
disease in itself is due to the lack of this protein. Probably several factor VIII specific T-cell clones have escaped the central tolerance and are present to cause a classical T-cell dependent activation of B cells, leading to ADA-formation, when the therapy starts.\textsuperscript{14,15} This is a considerable risk with replacement therapies, where genetic deficiency or a defect in the endogenous protein causes the disease. For HA patients with factor VIII treatment a high frequency of ADA, or inhibitors as they are termed in this field, is formed.\textsuperscript{15,16} These are predominately of the high-affinity immunoglobulin G (IgG) isotype, mainly of the IgG4 subclass, indicating a T-cell dependent B-cell activation.\textsuperscript{15} In accordance with that, the risk of ADA-formation is strongly influenced by the underlying factor VIII mutation, with higher immunogenicity seen in patients with nonsense versus missense mutations.\textsuperscript{15,17,18}

While it might not be unexpected that antibodies are formed against substances that the immune system has never encountered before, ADAs are also formed against proteins that we normally are tolerant against and which have been part of the central tolerance. This can be explained by a breaking of the peripheral tolerance. Since not all peptides of every self-protein can be expressed in thymus, a proportion of self-reactive T cells will still escape to the periphery. This is usually not a problem, since the peripheral tolerance ensures that naive T cells only become activated by dendritic cells (DCs) when they are provided with both the antigen specific peptide-HLA complex and proper co-stimulatory signals.\textsuperscript{20} DCs will trigger the help required for B cells to induce high-affinity iso- type-switched IgGs and efficient B-cell memory responses.\textsuperscript{21,22} Thus, individual variations, activation and regulation of lymphocytes and DC subsets might be most critical for ADA formation against injectable drugs.

Patients with MS that express normal levels of endogenous IFN\textsuperscript{β} protein receive treatment with an IFN\textsuperscript{β} homolog that they ought to be tolerant against, but yet ADAs are formed in these patients. In this case, two non-exclusive different mechanisms could be envisioned to be involved in ADA-formation, the T-cell dependent and the T-cell independent activation of B cells. The repetitive stimulation of DCs at the injection sites will eventually lead to the uptake and presentation of IFN\textsuperscript{β} peptides in lymph nodes by the DCs, a site where IFN\textsuperscript{β} do not appear normally. Therefore silent IFN\textsuperscript{β}-specific T-cell clones might be involved and can give the help that IFN\textsuperscript{β}-specific B cells need to become ADA producing cells. This T-cell dependent B-cell activation will lead to the high-titer ADA-production of antibodies with high affinity.

The T-cell independent B-cell activation can be induced by aggregates of IFN\textsuperscript{β} cross-linking B-cell receptors by repetitive structures.\textsuperscript{14,25} Although cross-linking of B-cell receptors in the first place leads only to the formation of low-affinity immunoglobulin M-antibodies, the presence of additional stimulating factors such as B-cell activating factor (BAFF) or interferon-\textalpha\textsubscript{2} are discussed to allow marginal centro B cells - the effector B cells of the T-cell independent antibody production - a limited switch to IgG, and potentially also the induction of memory responses.\textsuperscript{13,14} Both these mechanisms are probably involved when ADA is formed in IFN\textsuperscript{β} treated patients, although to different extent depending on the preparation, which will be discussed later.

Anti-TNF\textalpha\textsubscript{2} is an approved drug for RA and/or CD and include infliximab, etanercept and adalimumab. As infliximab is a chimeric murine-human IgG1 monoclonal antibody, the T-cell dependent B-cell activation toward a neo-antigen as outlined above might explain the comparable high immunogenicity (Table 1).\textsuperscript{18} Etanercept is a humanized IgG1 Fc fragment fused to two identical humanized TNF receptors, demonstrating lower immunogenicity.\textsuperscript{11} Nevertheless, for adalimumab, a purely humanized IgG1 antibody, conflicting data on ADA-frequency has been published [<1% to 87% (Table 1)],\textsuperscript{27} highlighting the fact that not only homology to human sequences, but also other risk factors discussed below as well as the ADA assay used, are critical to the reported immunogenicity.

Natalizumab, a humanized IgG4 antibody that targets the \textalpha\textsubscript{4}-subunit of two different

### Table 1. Immunogenicity of different biological pharmaceuticals.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Indication</th>
<th>Frequencies (%)</th>
<th>Clinical relevance and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>s.c.; i.v.</td>
<td>HA</td>
<td>0.33\textsuperscript{15,16,28}</td>
<td>Highly relevant, high frequency in patients with severe HA, LOR associated with potential life-threatening complications</td>
</tr>
<tr>
<td>IFN\textsuperscript{β}</td>
<td>MS</td>
<td>IA</td>
<td>28.47\textsuperscript{15}</td>
<td>Immunogenicity different for different IFN\textsuperscript{β}-preparations, high titers of NAb associated with LOR, role of low titer NAb or BAb controversial</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>MS</td>
<td>CD</td>
<td>2.4-6\textsuperscript{2,9,33}</td>
<td>Comparable low frequency in post-marketing studies, association with infusion-related side effects, testing highly standardized, assay does not detect monovalent antibodies</td>
</tr>
<tr>
<td>Anti-TNF\textalpha\textsubscript{2} BPs</td>
<td>RA</td>
<td>IFX</td>
<td>8.44\textsuperscript{10,34}</td>
<td>LOR and increase of the therapeutic dosage established for infliximab, association with infusion-related side effects, testing not standardized, concomitant treatment and dosage shown to highly impact frequency of ADA\textsuperscript{11}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eta</td>
<td>5.615\textsuperscript{18}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adalimumab</td>
<td>s.c.</td>
<td>&lt;1-87\textsuperscript{28}</td>
</tr>
<tr>
<td></td>
<td>INF</td>
<td>s.c.</td>
<td>6.76\textsuperscript{49}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>s.c.</td>
<td>2.5-17\textsuperscript{51}</td>
<td></td>
</tr>
</tbody>
</table>

HA, hemophilia; MS, multiple sclerosis; RA, rheumatoid arthritis; s.c., subcutaneously; i.m, intramuscular; MRI, magnetic resonance imaging; NAb, neutralizing antibodies; BAb, binding antibodies; CD, Crohn’s disease; LOR, loss of response; i.v., intravenously; *Frequency of NAb; °Persistent positives only.
Review

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53 Contaminants and process-related modifications can also contribute to immunogenicity, e.g. illustrated by the observation of a sudden increase in immunogenicity of a factor VIII preparation after changes in the production process. These factors can influence the amount of aggregates being formed.19

The mode and the frequency of administration

A higher frequency of administration increases the risk of ADA-formation compared with an acute therapy.19 The only once weekly intramuscular injected IFNβ-1a seems to carry the lowest risk of ADA-formation among the two different IFNβ-1a preparations.55 For factor VIII and IFNβ the subcutaneous administration is considered more immunogenic compared with the intravenous and intramuscular administration, respectively.55,56 This seems not to be true for anti-TNFα BPs, although this comparison is compromised by the chimeric character of infliximab (Table 1).

The genetics of the individual, and the diseases treated

The genetic influence in ADA-formation is evident when patients, due to a genetic deficiency, lack the expression of a normal endogenous protein. These patients are expected not to be tolerant to the BP, resulting in high rates of ADA-formation in severely affected patients with HA.57 However, also in tolerant patients the genetics influence the immunogenicity. Several genetic studies in different fields have shown an HLA association between different BPs and the formation of ADAs. The HLA molecules are highly polymorphic,58 and not all peptides of a drug will bind to all HLA alleles. Thus, both the amino acid composition of the drug, and the HLA haplotype of the patients are likely to influence the risk of developing ADAs. For MS patient treated with IFNβ, several associations between certain HLA class II haplotypes and ADA-development has been reported.52,59,60 Interestingly, the difference between the reported ADA-associated alleles, DRB1*04:01 and *04:08, and the protective alleles, DRB1*04:03 and DRB1*04:04, was only one amino acid in position 86 at the end of the alpha helix. This indicates that a single binding motif might have large impacts on which epitopes of IFNβ are presented. No difference was observed when looking at Bab and NAb separately, suggesting that the HLA-polymorphism might be important for triggering the presence of ADAs, but less important for the affinity maturation.29,60 Not only in MS, but also for factor VIII treated patients with HA, several class II HLA associations have been found, although these seem to be comparable weak.17 In addition, certain polymorphisms in non-HLA genes, such as TNFα, IL-10, and CTLA-4 in HA,53 or in proximity to a protein kinase gene and a gene involved in signal transduction pathways in MS patients treated with IFNβ, have been linked to ADA-formation.62

The HLA associations are probably highly dependent on the protein sequence of the BPs; thus, not necessarily the same HLA association can be expected to increase the risk of ADA-formation for different BPs, or different variants of a class of BPs. However, some of the non-HLA associations regulating ADA-formation could potentially predispose for developing antibodies against several BPs. Although this has not yet been studied in a comprehensive manner, at least in MS patients switched from IFNβ to natalizumab, no increased risk of ADA-formation toward both IFNβ and natalizumab were found, indicating different genetic susceptibility factors for ADA induction towards different BPs.63

The underlying disease of the treated patient might have an impact on ADA-formation. In HA, the causative factor VIII mutation strongly influences the risk of ADA (e.g. nonsense versus missense mutations).17 In addition, the excess bleeding is thought to give a state of chronic inflammation. This might result in a general unspecific activation of the immune system, increasing the risk of ADA-formation. This principal is supported by experimental data showing lower immunogenicity for factor VIII replacement therapy when animals were treated with the anti-inflammatory agent Hemooxygenase-1 (HO-1) before the injection.64 Similarly, one can hypothesize that IFNβ, which in itself stimulates the immune response, and the heightened inflammation status of MS patients, both to some extent contribute to the risk of ADA-formation.

Concomitant medication and the dosage of the biological pharmaceutical

Mainly for TNF-antagonists the dosage as well as the administration of concomitant medication - such as methotrexate - has been shown to impact immunogenicity. Higher dosage might induce tolerance, and immunosuppressive co-medication suppresses the activation of antibody-producing B cells, both resulting in lower ADA frequency.51 In MS the combined administration of IFNβ and pulse methylprednisolone therapy can reduce ADA development in IFNβ naïve individuals.65

Methods to detect anti-drug antibodies

The difference in ADA frequencies reported for the same BP in different studies can also be explained by the method used to detect the antibodies (Table 1). Assays for determining sero-prevalence and immunogenicity need to detect all binding ADAs, but also to assess the frequencies and quality of their neutralizing capacity.

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Typically, immunoassays are used to screen for ADAs. Samples tested positive in the immunoassay for ADAs are subsequently tested in an in vitro cell-based bioassay or a non-cell based competitive ligand binding assay to determine the neutralizing capacity.

General assay principles for screening of anti-drug antibody presence

Conventional screening assays such as enzyme linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) are widely used for detection of ADAs. ELISAs are rapid, robust and easy to perform, allowing for high throughput screening. Different methods such as direct, indirect, and bridging ELISAs can be applied. In the bridging assay the antibody is captured by the solid-phase-bound antigen and visualized by the labeled antigen. Since the antibody is recognized twice this results in higher specificity. This can be applied with or without radioimmunolabeling. A disadvantage of the bridging ELISA and radiolabeling techniques, however, is that they cannot distinguish between BAbs and NAb. Therefore, these assays cannot tell what percentage of the antibodies detected are neutralizing and actually have direct implications on the binding of the drug to its target. Moreover, the restricted use of radioactivity limit the use of the RIA assays in clinical routine testing.

General principles of neutralizing antibody assays

In vitro neutralizing antibody assays are the methods that characterize the ability of ADAs to antagonize the biological effect of a BP. For most of the BPs, NAb are currently studied in cell-based bioassays in which treated cells respond directly or indirectly to the BP in a dose-dependent manner and then this reaction is blocked in presence of the patients sera if these contain neutralizing ADA. Readouts will be different for various assays (e.g. proliferation, apoptosis, or mRNA expression), and the design needs to reflect the agonistic or antagonistic character of the BP. One example for a recently developed cell-based technique is the luciferase reporter gene-expression assay. In this method a cell-line is used in which a firefly luciferase gene is coupled downstream to the promoter region of the target of interest lying downstream of the receptor stimulated by the drug. In case NAb are present in the serum of the patient, they will interfere with e.g. a blocking BP such as a TNF-antagonist, which consequently will result in a higher luciferase activity induced by added soluble TNF. Whatever system is used to study NAb, an extensive validation is required to acquire reproducible and reliable analyses for clinical routine. As cell-based assays are time-consuming, attempts to replace these assays with non-cell based competitive ligand-binding assays to study the neutralizing capacity of ADAs are considered for some of the BPs.

Examples of techniques currently used in hemophilia, multiple sclerosis, rheumatoid arthritis and Crohn’s disease

The inhibitors in HA are predominantly measured by the Bethesda quantitative assay and the Nijmegen assay. In both techniques the residual factor VIII activity is quantified after mixing a patient plasma sample with plasma containing a standardized defined amount of factor VIII. Binding and neutralization assays are subsequently applied to detect ADAs to IFNβ in patients with MS. Direct ELISAs are most commonly used in the first step to detect BAbs present in the serum of patients, although bridging or double antigen ELISA techniques have been recently described. However, these assays detect ADA in up to 70% of the patients which does not necessarily reflect their clinical relevance. Therefore several cell-based bioassays have been developed to determine the neutralizing capacity of BAbs. The most widely used techniques study the inhibitory effect of IFNβ in the presence of patient sera on the viral cytopathic effect (CPE), or the mRNA or protein expression of the IFNβ responsive gene myxovirus resistance protein A (Mx1). In patients with MS or CD natalizumab ADA is detected with a bridging ELISA screening. Serum samples that are tested positive for antibodies can further be evaluated regarding their neutralizing capacity in a cell-based blocking approach. However, due to a high concordance rate between the two assays, only the bridging ELISA step is used in clinical routine.

So far ADA testing is not integrated into clinical routine for treatment of RA or CD with anti-TNF-antagonist, mainly because BAbs have not yet consistently been associated with LOR. Experimental ADA-testing includes ELISA and RIA methods to screen for ADA (Table 1). Most of these tests also include studying drug levels in parallel to assessment of the functional relevance of ADAs. Recent cell-based assay such as reporter gene methods are currently evaluated regarding their predictive value for LOR.

Strategies to deplete persisting anti-drug antibodies

Antibody concentrations can be reduced by plasma exchange or immunoadsorption. In conditions where the LOR is associated with fatal consequences and long-term therapy is required, such as in HA – strategies aiming to induce tolerance to the BP have already been developed. High doses of factor VIII are given for selected immunogenicity studies in vivo cell assays, non-human primate, or transgenic mouse models are used. Main goal in these models is to be able to already preclinically predict the effect of protein sequence, route of administration, or concomitant medication on immunogenicity, and the clinical relevance of ADA-formation. Furthermore, animal models are useful tools to further elucidate the mechanisms of ADA-induction. The analysis of expanded T-cell libraries, and transgenic mouse models for human HLA, currently explored to predict epitopes for efficient vaccines, are promising recently developed tools to predict immunogenicity. Ex vivo studies include the quantitative analysis of the CD4+ T-cell repertoire regarding specificity to the therapeutic agent.

To predict the risk of ADA-formation in the individual patients treated, genetic analyses might be promising future approaches. Other biomarkers include e.g. phenotyping the T and B cells as well as DC subsets and future studies will show the prediction value of these phenotype characterizations for ADA-development.

Prediction and prevention of anti-drug antibody formation

In drug development, measures to predict and prevent immunogenicity of a new compound have been developed. Attempts to lower the immunogenicity for e.g. IFNβ variants by the elimination of an immune-dominant epitope have not yet been successful. However, many improvements in drug formulations have efficiently reduced the immunogenicity of IFNβ. Other strategies have been to reduce the aggregate formation, with as simple approaches as improved storage and handling of the protein product by clinicians and patients.

For selected immunogenicity studies ex vivo cell assays, non-human primate, or transgenic mouse models are used. Main goal in these models is to be able to already preclinically predict the effect of protein sequence, route of administration, or concomitant medication on immunogenicity, and the clinical relevance of ADA-formation. Furthermore, animal models are useful tools to further elucidate the mechanisms of ADA-induction. The analysis of expanded T-cell libraries, and transgenic mouse models for human HLA, currently explored to predict epitopes for efficient vaccines, are promising recently developed tools to predict immunogenicity. Ex vivo studies include the quantitative analysis of the CD4+ T-cell repertoire regarding specificity to the therapeutic agent.

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ments, when ADA formation is not a potentially life-threatening consequence. Therefore, ITT is not generally considered a practical alternative for drugs that modulate the immune system (e.g., IFNβ), although in a pilot study of high doses of i.v. administration of IFNβ, the bioavailability could be restored. These studies, however, are complicated by the fact that a proportion of patients spontaneously revert to negativity and also regain the clinical effect of the drug, mainly seen in patients with low-positive titers. Other strategies, such as methylprednisolone alone or in combination with azathioprine did not have a significant effect on the titer courses in small scale studies and short trial periods of six months. Conversely, in the treatment of CD with infliximab the co-medication with azathioprine or methotrexate was associated with a lower risk of ADA-formation.

Conclusions

Development of ADA is an immunological phenomenon that has to be taken into account in modern medicine. In some fields this is a well-established routine of treatment surveillance, but not in others. The first obvious task to improve the value of immunogenicity studies in clinical practice is a higher level of standardization of ADA testing methods. The different frequency of ADAs reported for different BPs, and in particular for the same BPs in different studies (Table 1), illustrates the complexity of measuring immunogenicity, compromised by different trial design, study populations, assay techniques, timing of measurements, mode of administration and concomitant immunosuppressive medication. Measurement of anti-natalizumab antibodies with one highly standardized method results in comparable frequencies in post-marketing studies across different populations. Nevertheless, also for this test methodological improvements can be discussed, as a bridging ELISA might not detect monovalent IgG4 antibodies that potentially affect the pharmacokinetics of the drug in some individuals.

Clearly, the clinical relevance of ADAs to BPs differs across the clinical fields. Therefore, the issues of prevention, prediction, and depletion of ADAs have received varying attention. In HA, where factor VIII treatment is a unique therapy for a life-threatening disease, the acceptable treatment risk might be higher, and cost-intensive efforts are warranted to deplete ADAs. Conversely, although IFNβ is still first line treatment for patients with MS mainly due to the positive safety profile, various new therapeutic options currently become available. Thus, not the depletion but rather the prevention of the LOR due to immunogenicity is an important aim in this field. Importantly, a consensus has already been achieved that patients with high titers of NABs should be switched to non-IFNβ treatments in several countries. However, due to a still existing lack of standardization in ADA testing protocols the cut-off to define high titers of NABs considerably vary across different centers.

In particular for anti-TNFα BPs, immunogenicity assays seem to produce controversial data, only partly being able to correlate LOR to the presence of ADAs. Techniques need to be established which are able to detect the quantitative and qualitative appearance of ADA in first hand and then secondly in what way this correlate with LOR. Only then, clinicians can decide based on a meaningful result if alternative anti-TNFα BPs could be an option, or a different class of BPs should be tried.

Taking together, our examples from clinical practice illustrate the need of further research on immunogenicity against drugs across different fields in multicenter approaches to standardize assays and to help to predict LOR due to immunogenicity. This could contribute to prevent that a large proportion of patients is exposed to an expensive, but ineffective and potentially harmful therapy.

References


[Drugs and Therapy Studies 2012; 2:e11]


