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To cite this article: Andrea Matucci, Francesca Nencini, Enrico Maggi & Alessandra Vultaggio (2019): Hypersensitivity reactions to biologics used in rheumatology, Expert Review of Clinical Immunology, DOI: [10.1080/1744666X.2020.1684264](https://doi.org/10.1080/1744666X.2020.1684264)

To link to this article: <https://doi.org/10.1080/1744666X.2020.1684264>



Accepted author version posted online: 22 Oct 2019.



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Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Clinical Immunology*

DOI: 10.1080/1744666X.2020.1684264

Hypersensitivity reactions to biologics used in rheumatology

Andrea Matucci^a, Francesca Nencini^a, Enrico Maggi^b and Alessandra Vultaggio^a

^a Immunoallergology Unit, Dept of Medicine and Geriatrics, Careggi University Hospital, Florence, Italy

^b Translational Immunology Unit, Immunology Area, Pediatric Hospital Bambino Gesù, I.R.C.C.S. Rome. Italy

Corresponding author;

Dr Andrea Matucci

University Hospital Careggi Ringgold standard institution - Dept of Medicine and Geriatrics

Firenze, Toscana, Italy

andrea.matucci@unifi.it

Article highlights

- Biological agents are structurally immunogenic and induce a complete cellular and humoral immune.
- Anti-drug antibodies impact the drug efficacy and/or induce hypersensitivity reactions
- The development of anti-drug antibodies is an early phenomenon.
- A proportion of infusion reactions are associated with the presence of anti-drug IgE antibodies
- Acute infusion reactions may also be sustained by antibody-independent mechanisms

Accepted Manuscript

Abstract

Introduction: Biological agents (BAs) target disease mechanisms and have modified the natural history of several immune-mediated disorders. All BAs are immunogenic, resulting in the formation of anti-drug antibodies (ADAs), which can neutralize drug activity leading to loss of response and potential relapse. In addition, ADAs can also cause serious adverse events such as infusion hypersensitivity reactions (HRs).

Areas covered: This review discuss the recent knowledge on the effector and regulatory mechanisms involved in the immune response to BAs used in patients suffering from rheumatic diseases leading to the production of ADAs and the impact on clinical outcome. Specifically, the demonstration of the involvement of specific T cell responses underline B cells activation and ADAs production are discussed correlating them to the different possible clinical consequences.

Expert opinion: Although the mechanisms of the immune response and specifically the ADAs production to BAs have been extensively clarified in the last years, as well as their capacity to impact on clinical outcomes, among clinicians today a low awareness and in some cases a rejection persists, not only of the analysis and understanding of the immunological mechanisms behind the immunogenicity of BAs, but also the possible clinical impact that this may have.

Key words: Anti-drug antibodies; Biologic agents; Monoclonal antibodies; Infusion reaction; Immunogenicity; IFX-specific T cells; IgE-ADA

1. Introduction

Novel treatments targeting the disease mechanisms, referred to as biological agents (BAs), including recombinant cytokines, monoclonal antibodies (mAbs) and fusion proteins, in the last years have modified the natural history of several immune-mediated disorders including rheumatic diseases. Among the latter, in addition to the well known group of anti-tumor necrosis factor- α agents (infliximab, adalimumab, golimumab, certolizumab and etanercept), several other biological agents have been introduced such as tocilizumab [anti-interleukin (IL)-6Receptor], belimumab [anti-soluble B lymphocyte stimulator (BLyS)], anakinra and canakinumab (IL-1R antagonists), abatacept (anti-CTLA/CD28). As these agents become more widespread in their use particularly in rheumatic diseases, it is becoming increasingly important to be prepared to manage adverse reactions associated with their use [1]. In fact mAbs, as other BAs, are structurally immunogenic, even though usually they elicit a minor, subclinical and transient phenomenon, but, sometimes, these drugs induce a complete cellular and humoral immune responses which impact the drug efficacy, in other words induce loss of response or stimulate hypersensitivity reactions (HRs) [2,3]. In fact, a proportion of patients do not respond to treatment with a mAb at all (primary failure) but in a proportion of them, following an initial good response, the clinical efficacy is lost over time (secondary failure) due to the production of anti-drug-antibodies (ADA) capable of neutralize or increase the clearance of the drug. The loss of response, more frequent in comparison to HRs, may be explained by formation of immune-complexes between mAbs and ADAs, leading to their increased clearance reducing the half-life and serum level or by the inhibition of the drug activity by blocking the active site for target recognition (neutralizing ADAs) [4, 5].

Concerning the HRs, the safety of therapeutical mAbs represents an important topic in clinical practice as well as a new field of research by considering their growing number and expanding clinical applications. This review will discuss the recent knowledge on the effector and regulatory mechanisms involved in the immune response to BAs used in rheumatic patients leading to the production of anti-drug antibodies (ADA) and the relationship with the drug-induced HRs.

2. Immunogenicity and specific immune response to BAs

The induction of a specific immune responses to BAs can substantially fall into two mechanisms: a) the activation of an adaptive immune response to non-self epitopes expressed by the drug in a way similar to the response elicited by pathogens or exogenous toxins and, b) the loss of immunotolerance as observed in autoimmunity. The majority of humoral response to therapeutical mAbs is due to an adaptive response to foreign antigens, leading to the expansion of both memory T cells and adaptive T regulatory (Treg) cells and of B cells specific for non-self epitopes [6,7]. The break of B and T cell tolerance to autologous proteins present in the majority of treated patients, can contribute in different ways to improve the drug immunogenicity. The sequence of events leading to B cell activation and ADA production can follow a T cell-independent- or dependent- fashion. The former occurs when some structural sequence of the drug (namely polymeric repeats or protein aggregates) induces the signals required to directly stimulate B cell subsets [8] (Fig. 1). This mechanism is often cited as a source of ADA of IgM isotype usually not leading to affinity maturation or generation of memory B cells. By contrast, T cell-dependent B cell activation results in a more robust antibody response, isotype switching and induction of memory B cells [9,10].

The prevalent induction of high affinity ADA of IgG class and, in particular, of IgG1/IgG4 subclasses reinforces the concept that BAs prevalently act as a T-dependent antigens [11,12].

Concerning infliximab (IFX), a peculiar example of mAb with high immunogenicity profile, it has been shown, irrespective to the diseases, an early development of ADA, mainly within the first 6 months of treatment [3,5,13]. In addition, patients who resulted ADA negative from 12 months till many years of treatment display poor or no risk of developing ADA suggesting that an active regulatory mechanism is persistently operating [13]. Several mechanisms are likely responsible for explaining the immuno-tolerance to BAs: first, the induction of adaptative Treg cells to non-self epitopes expressed by BAs (possible allotypes) which are usually associated with the parallel onset of memory T cells to the same epitopes in secondary lymphoid organs [7]. Second, the so-called high-dose tolerance induced by high BA doses, usually involving anergy and immune deletion mechanisms, is likely responsible for the T cell unresponsiveness to therapeutical BA [14]. Lastly, since BAs share many self antigen with Ig, they can induce the contemporarily amplification of

natural Treg cells specific for such antigens [15]. In this context, it has been shown that some sequences located in the Fc and Fab domains of human IgG exert a central role in immunotolerance. These epitopes, called Tregitopes have been found to selectively expand Treg cells, but not T effector cells. In vitro they specifically activate CD4⁺ T cell, expressing CD25/Foxp3 and increase the production of regulatory cytokines and chemokines [16]. If co-administered with non-self antigens, Tregitopes present on the human part of BAs may be responsible for tolerance to idiotypic epitopes of the therapeutic mAbs [17].

The superior clinical efficacy of anti-TNF therapy in combination with immunomodulators such as methotrexate or thiopurine as compared to monotherapy is well-established for IFX and, but less evident, for adalimumab [18]. Experimental data have suggested that the addition of an immunomodulator to anti-TNF monotherapy can modulate ADA production and recapture clinical response in IBD patients. It was demonstrated that azathioprine has the ability to delete memory T-cell clones after repeated antigen exposure. This mechanism may explain why it is possible to decrease ADAs levels due to the decrease of T-cell memory responses to anti-TNF agents [19].

Different ADA isotypes have been observed during biological treatment: IgG, mostly of IgG1 and IgG4 subclasses, but also IgE, IgM, and IgA [12, 20,21]. Sustained production of IgG ADA is involved in the majority of adverse events. BA-specific IgE have also been shown to cause immediate HR, and low affinity and early-stage transient IgM capable of activating the complement system, has been also reported [20-23].

Concerning IFX and adalimumab largely used in rheumatic diseases, other regulatory mechanisms can be underlined. In fact, these two mAbs not only interfere with serum TNF- α but also act as a reverse signal on membrane TNF α -bearing cells by inducing tolerogenic dendritic cells (DC) producing IL-10, Notch 1 upregulation mediating inhibition of T cell cycle and apoptosis [24,25]. A specific adaptive immune response towards BAs is also suggested by the observation that the re-exposure to a second cycle of drug (after a long period of interruption) triggers the quick onset of IgG (and also IgE) ADA often leading to a severe HR. This trend looks like a secondary immune response, the primary sensitization likely occurring during the first course of treatment [26,27]. This also suggests that tolerance to BAs operating during the

first course of therapy is transient and slower to be elicited by the drug than memory T effector cells after a period of lack of antigen stimulation (Fig.2).

The pathogenic mechanisms involved in immediate HRs to mAbs might be related to the direct release of cytokines (cytokine releasing syndrome –CRS-) [28,29]. Reactions due to CRS typically occur on the first administration, as the consequence of the rapid destruction of cells targeted by the mAb through complement-mediated and/or antibody-mediated cell death leading to the release of pre-formed cytokines such as TNF- α and IL-6 [30,31]. The CRS is more frequent in patients suffering from B cell lymphomas due to the high amount of cells targeted by mAbs as rituximab, a mechanism similar to that observed with anti-CD19 CAR-T cells used in the same disorders [32,33]. However, in patients suffering from rheumatic diseases, ADA-induced HRs are more frequent taking into account the reduced ability to develop Treg cells in these patients and the high immunogenicity of anti-TNF- α . Specifically recently we provided clearcut evidence that IFX leads to an adaptive (cellular and/or humoral) immune response in all exposed patients irrespective to their basic autoimmune diseases [5].

3. Correlation between ADAs and HRs

HRs to BAs can result in anaphylaxis, a life-threatening condition due to massive activation of mast cells (MC) with subsequent release of powerful preformed mediators responsible for symptoms [34].

The development of ADAs has been linked to infusion reactions for many years and driven therapeutic strategies to reduce the risk of these adverse events have been proposed, such as co-treatment with immunosuppressor, premedication, ongoing treatment. However, not every study has confirmed the link between HRs and ADAs; in some studies, only 30% of patients with infusion reactions had ADAs [35,36]. The pathogenesis of BA-related acute HRs has not been yet completely defined. A specific classification has been proposed on the basis of the underline mechanisms, including IgE- and non IgE-mediated reactions (type β) and CRS (type α) [37]. Type I reactions, is characterized by a preliminary phase of sensitization during the the first exposure to the drug in which a Th2 response occurs with the onset of IgE production [38]. During the re-exposure, the drug epitopes are recognized by the cell-bound IgE and elicit the release

of mediators by tissue MC and circulating basophils which promote allergic symptoms. Thus, the reactions does not occur during the first infusion of the drug, except when pre-existing cross reacting IgE are detectable as in case of cetuximab a mAb largely used in oncology [39]. A pre-existing sensitization to xenogenic (murine) antigens or to drug excipients are further mechanisms accounting for type I reactions at the first infusion of BAs [40].

The acute infusion reactions to IFX are usually associated with the presence of high titers of IgG ADA [41]. However, a proportion of IFX-related reactions (27%) are associated with the presence of IgE isotype [23]. ADA of IgE isotype have been described in a proportion of ADA+ patients who develop more severe HRs, and are closely associated with drug-specific skin test positivity [20]. In fact, IgE positive patients also resulted positive to skin test, thus confirming the biological activity of these Abs [23]. Noteworthy, a correlation between HRs and the presence of IgE ADA or positive skin tests has been reported for several mAbs [42,43].

Taking into account that IgE-ADA is rarely detected in IFX-treated patients and that the assays used are generally not optimised to measure IgE specific to therapeutic antibodies, some Authors believe that most infusion are not associated with IgE-ADA [44,45]. The reported incidence of ADAs formation, varies widely depending on the assay used [46,47]. Furthermore, some laboratory issues must be considered taking into account that the low frequency of ADA positivity, including IgE, may be related to drug interference in the assay and/or the low affinity of ADA, both leading to an underestimation of the number of ADA+ patients. ADA can be detected only when the production of ADA exceeds the amount of circulating drug avoiding the false negativity due to ADA–drug immunocomplexes [48]. Explanations for these discrepancies have been proposed, as the sensitivity of different assays to detect ADA or the different timing of ADA detection during the course of therapy. On the other hand the positive results of skin testing in patients who experience an immediate HR, although have not already been standardized, confirm the activation of mast cells through an IgE-dependent pathway [20,23,49,50].

The IgE-mediated anaphylaxis usually associates the increase of serum tryptase, the mediator accounting for mast cells activation. However, in a cohort of several IFX-reactive patients, serum tryptase levels were in

the normal range after the reaction [51]. The normal value of serum tryptase does not exclude an IgE-mediated mechanism and this occurs also in the majority of patients with food-induced anaphylaxis [52]. In these patients, the involvement of basophils has been hypothesized since these cells express the FcεRI and, upon IgE triggering, release mediators (as the MC), but not tryptase [53,54]. Circulating basophils can be the first cells triggered by intravenously administered mAbs. Finally, both IgE ADA and skin test positivity disappear very early after the HR and this result must be considered to avoid oversimplification on the possible pathogenic mechanisms involved [20,41].

In addition to IgE ADA, also IgG ADA could be involved in the induction of HRs. Murine models revealed that anaphylaxis also occur through another pathway including IgG, FcγRIII, macrophages and basophils and the Platelet Activating Factor (PAF) release [55]. Whether an IgG mechanism may be relevant in human anaphylaxis remains an open question. Indeed, very high titers of IgG ADA have been detected in patients who experienced anaphylaxis during IFX infusion [41]. The presence of IgG-positive (IgE-negative) ADA+ patients with severe HR, strongly suggest a role for IgG ADA as the main mechanism of BA-induced anaphylaxis also in humans [20].

The presence of a complex immunological mechanism of HR to IFX is also suggested by the demonstration of high levels of IgG4 ADA in IgE ADA+ patients [11]. Notably, the presence of IgG4 response to IFX, which is associated with the production of IgG- and IgE-ADA, is not protective against immunogenicity-related events such as HRs and LOR [11].

Several studies in murine models have proven the possibility of an IgE-independent anaphylaxis due to the participation of IgG ADA, C' cascade activation, FcγRIII engagement, macrophages or basophils activation and involvement of platelet activating factor (PAF) [56,57]. In humans, anaphylaxis in IgG-ADA positive patients has been described, and seems to be more relevant when large amounts of antigen are used and high levels of IgG ADA are induced [56].

4. Clinical manifestation of HRs to BAs

HRs may be divided into local and systemic and in acute and delayed. Acute infusion reactions occur during or within 1 h after infusion, whereas delayed reactions occur from 1 h to 14 days [37]. The epidemiological data of HRs to mAbs are very heterogeneous due to the broadness of the definition for infusion reactions and ranging from 3-5% to over 70% for rituximab [56].

The clinical manifestations of both acute and delayed reactions vary considerably, ranging from mild to severe and life-threatening, thus important clinical consequences such as dropout therapy or fatal cases may occur. Among acute HRs, anaphylaxis represents the most severe event which may occur, characterized by respiratory distress, flushing, pruritus, laryngeal edema, bronchospasm, accompanied by skin, gastrointestinal, and cardiovascular involvement. Acute infusion reactions may also occur at the first dose or during the course of treatment, thus suggesting different underlying pathogenic mechanisms. In fact, they may be sustained by an antibody-dependent or independent pathogenic mechanism. It is important to underline that among ADA-mediated HRs, IgE- and IgG-mediated reactions may be clinically indistinguishable. On the other hand, among non-ADA dependent reactions, the so called cytokine release syndrome (CRS) due to a massive release of cytokines is a well known clinical event. From a clinical point of view the manifestations of ADA-mediated reactions and CRS partially overlap, even though fever, headache, myalgia are more frequent in CRS. Furthermore, in contrast to ADA-mediated hypersensitivity, CRS may be managed by short-term cessation of the BA infusion and reduction of the rate infusion after restarting [58]. Hypersensitivity reactions, particularly CRS, may be prevented or at least attenuated by pre-medication with anti-histamines and steroids. However, at least in our experience pre-medication do not prevent ADA-mediated HRs particularly when IgE ADAs are involved [23].

Delayed infusion reactions can occur with a range of symptoms [macopapular rash, cutaneous vasculitis, drug eruption with eosinophilia and systemic symptoms (DRESS), Steven-Johnson Syndrome, TEN, etc.], not only with i.v- but also with subcutaneous BAs, largely used in rheumatic patients. The most common manifestation of a non-immediate HR to mAbs is the serum sickness-like reaction starting typically from 5 to 7 days after infusion and it may present with fever, malaise, arthralgia/arthritis, jaw pain or tightness, an erythematous (sometimes urticarial) skin eruption, purpura [59,60].

5. HRs and Tumor Necrosis factor- α inhibitors

In the last years, the large use of TNF- α blockers in rheumatic patients has allowed to collect epidemiological data on infusion reactions to these drugs [56]. Among the anti-TNF- α drugs the immunogenicity is deeply influenced by amount of xenoantigen included in the therapeutic molecule. Chimeric mAbs (-ximab) such as infliximab and rituximab, made from variable regions of a murine source and constant regions of a human immunoglobulin, may contain sequences (xenoantigens) recognized as nonself epitopes and stimulate immune response. Humanized mAbs (-zumab) as tocilizumab, but not included among anti-TNF- α , and fully human mAbs (-mumab) as adalimumab, golimumab, belimumab are generally less immunogenic. The anti-TNF agents IFX, etanercept, adalimumab, golimumab, and certolizumab are all quite different in composition and structure, with resulting differences in immunogenicity [61]. In fact, unlike adalimumab and golimumab, IFX being a mouse–human chimeric IgG1 mAb the mouse moiety is thought to be the source of IFX's higher immunogenicity [62]. However, all the biologicals, including fully human proteins, have the potential to induce immunogenicity leading to the development of specific ADAs [63].

Concerning the Fc fusion proteins, these drugs include few new epitopes, thus explaining their low degree of immunogenicity, as observed with etanercept [64]. Regarding certolizumab pegol actually considered with low immunogenicity profile at least partially due to the variations in assays used, recent studies showed that long term treatment with this biological agent is associated with a transient or persistent production of ADAs the latter associated with a loss of response rather than HRs [65-67].

Overall, the frequency of adverse events to IFX in a large panel of patients is low, occurring in 4,8% of Rheumatoid Arthritis (RA) and in 1% of Psoriatic Arthritis [68]. As previously mentioned, patients with anti-infliximab ADA are at increased risk of immediate HRs compared with patients without such antibodies [69]. The prevalence of ADA to IFX, ranging from 10% to 60% of patients, reflects several variables: the different diseases, the concurrent medications, the timing of sampling, the disease activity and duration, the doses of administered drug and the assays to detect ADA [70]. Type I infusion reactions to IFX usually occurred from the third to the sixth infusion [16]. Moreover, in these patients we showed a significant

relationship between the presence of ADA and the acute reaction, its early onset, the frequency and severity directly correlating with ADA titers [13,20].

In clinical setting it is important to underline that ADA appear to be specific for each drug, with no cross-reactivity between BAs. However, it has been shown that patients who develop anti-IFX ADA, when are treated with adalimumab are more prone to develop ADA to this second mAb, even though they associated with a higher treatment failure rate than a HR development [71]. The high immunogenicity profile of adalimumab is confirmed by the data showing that in patients with highly active RA receiving this mAb, 87% showed ADA development. [72]. Moreover, anti-adalimumab ADA result in functional neutralization of the drug, thereby providing a mechanism by which ADA formation mainly leads to loss of response and limited adverse events [71,72].

Finally, an emerging issue is related to the introduction on market of biosimilars for anti-TNF- α agents. For IFX, it has been shown that anti-infliximab ADA cross-react with the corresponding biosimilar and their administration in patients with previous HR to the originator is not recommended [73].

6. HRs and non-Tumor Necrosis factor- α inhibitors

Among non anti-TNF- α agents, largely used for treating rheumatic diseases, rituximab (RTX), a chimeric anti-CD20 mAb, is frequently responsible of immediate HRs occurring at the first exposure, particularly when used in patients with lymphomas [30,32], but less in those with RA [74]. As previously underlined, the large majority of these reactions are consistent with a CRS caused by massive B-cell lysis [48]. Generally the rituximab-induced CRS are mild or moderate in their severity, rapidly disappearing by reducing the rate of infusion and not recurring at the second administration. Even though CRS is the main mechanism involved in HRs to RTX, the presence of drug-specific Th2-type cells and IgE antibodies has been demonstrated, thus suggesting that type I hypersensitivity may be an additional mechanism to CRS in the development of RTX reactions [29].

Tocilizumab, a humanized mAb that binds to circulating soluble interleukin-6 receptor (IL-6R) and membrane-expressed IL-6R, blocking IL-6 proinflammatory activities. Immediate HRs to tocilizumab are

rare although several cases of anaphylaxis have been reported. The positive skin testing for tocilizumab in a proportion of patients supports an involvement of an IgE-mediated mechanisms [75,76].

More recently the availability of a new biological agent as secukinumab, a fully human anti-interleukin-17A monoclonal antibody, have raised the discussion on the immunogenicity profile resulting very low, below 1% in all treated patients [77,78]. Among biological agents largely used in rheumatic diseases it should be also remembered the antagonists of IL-1 as anakinra and canakinumab, the anti-BLyS belimumab largely used in patients suffering from lupus erythematosus and more recently the anti-IL-5 receptor α chain benralizumab used in Eosinophilic Granulomatosis with Polyangiitis (EGPA) formerly named Churg-Strauss Syndrome other than in patients suffering from severe eosinophylic asthma [79-82].

Concerning the anti-IL-1 antagonists, ADAs to anakinra were more frequently associated with lack of efficacy in patients who tested positive for neutralizing antibodies while the association between ADA to anakinra and adverse events was not reported [83].

Canakinumab displayed a low immunogenicity profile and none of the ADA-positive patients experienced treatment failure or exhibited antibody- HRs [84,85].

Belimumab, now largely used in systemic lupus erythematosus particularly in patients with tested positive for anti-DNA antibodies and articular involvement, also displayed a low immunogenicity profile with a rates of serious infusion reactions (including hypersensitivity reactions) occurring less than 1% of the patients [86].

7. Conclusions

The production of ADAs has been consistently linked to diminished clinical improvement and loss of response with several BAs including those use in rheumatic patients. Although of less importance in terms of frequency, the immunogenicity of BAs has been also associated with an elevated risk of acute systemic HRs, particularly with infliximab. Certainly, all BAs including fully human mAbs have the potential to induce immunogenic reactions. Of the currently available anti-TNF agents, infliximab and adalimumab appear to have the greatest immunogenicity associated, however, with an increased incidence of HRs only for IFX,

whereas etanercept appears to have very low immunogenicity as the other non-anti-TNF agents as tocilizumab and abatacept. It is important to keep in mind that not all HRs are ADA-mediated and other mechanisms can be involved as in the case of rituximab which cause the CRS during the first infusion. Concerning ADA it has been clearly shown that a close relationship between the timing of ADA appearance and HRs exists and specifically in all ADA+ patients who experienced an infliximab-related infusion reaction, ADA development anticipates HRs. More difficult is to explain why the production of ADA to adalimumab is associated with HRs in a minor proportion of patients. Possible explanations are related to the fact that ADA to adalimumab are mainly IgG neutralizing anti-idiotypic antibodies, do not activate complement system and the drug is administered subcutaneously. There is still a lot to be learned concerning the pathogenic mechanisms involved in HRs to BAs. The role of IgE ADAs is still a matter of debate and there is little consensus on detection method standardization, definition of cut-off values for defining the presence of different ADA isotypes. However, the demonstration of the involvement of specific T effector and regulatory T cell responses underline B cells activation and ADAs production, both IgE and non-IgE, have been extensively provided. These data open the way for future strategies for monitoring immunogenicity and prevent adverse events to BAs. Finally, from clinical point of view, patients who developed HRs in which no alternative therapeutic strategies are available, drug desensitization is a procedure that allows temporary clinical tolerance to a drug, by administering increasing amounts to complete the therapeutic dose.

8. Expert Opinion

Biological agents target disease mechanisms and have modified the natural history of chronic immune-mediated diseases, among them rheumatic disorders. Biological agents are structurally immunogenic, and therefore are able to elicit complete cellular and humoral immune responses. Patients who develop an immune response against the biological agent, which results in the formation ADA, correlates with lower

serum drug levels, reduced clinical response and, in a low proportion of them, in HRs although minor or subclinical and transient phenomena are the rule [3, 87-89].

Patients who develop ADA-dependent HRs, particularly with IFX, frequently also displayed loss of response to treatment.

An anti-drug (BAs) immune response probably occurs in most, if not in all, patients treated with therapeutic antibodies, for which the definition of the mechanisms of tolerance including the induction of adaptive T-regulatory cells, represents major progress towards managing better the treatment with BAs in terms of efficacy and safety. While the detection of a specific T-cell response is currently confined to the search field, monitoring antibodies against therapeutic antibodies is routinely applicable and may lead to more rational treatment strategies to improve efficacy and safety. For that reason, another important area of future research is the optimization and comparison of assays to detect the different isotypes (IgG and/or IgE) of ADAs. The correct assay design, specificity, inclusion of appropriate controls, and performance of the assay are essential for accurate and reproducible data to be obtained. When we discuss HRs and specifically acute forms, it is mandatory to clarify the possible role of *in vivo* tests and their diagnostic performance in identifying patients at risk of anaphylactic reactions. In fact, beyond the discussion and conflicting results of different *in vitro* assays for detecting IgE ADA, positive skin testing reflects IgE-mediated mast cells activation and represents a good diagnostic tool in the diagnosis of HRs to BAs (if performed without a delay of several months after the adverse event because skin testing positivity has been shown to disappear quickly over time). In addition, physicians must be aware that previous mild infusion reactions to BAs can be followed by subsequent severe HRs to the same drug. In these cases a complete ADA screening must be performed before the administration of the same BAs.

Certainly, among BAs used in patients suffering from rheumatic diseases, we must underline the different immunogenicity profile of some of them such as infliximab and adalimumab in comparison to the others, as well as the factors influencing the ratio between regulatory and effector responses affected by patient-related (disease activity; rheumatoid factors and anti citrullinated antibody positivities; re-treatment; etc) and drug-related factors (dose; route of administration; structure of mAb; fusion proteins; etc). High-dose

tolerance, involving anergy and immune deletion, is likely responsible for the nonresponsiveness of T cells to therapeutic BAs. The interruption of treatment for a long period may lead to the loss of tolerance and expose the patient at risk of HRs in case of re-treatments due to the expansion of a rapid effector response with ADA production.

Although the mechanisms of the immune response and specifically the ADA production to BAs have been extensively clarified in the last years as well as their capacity to impact on clinical outcomes in terms of loss of response and adverse events, among clinicians today a low awareness and in some cases a rejection persists, not only of the analysis and understanding of the immunological mechanisms behind the immunogenicity of BAs, but also the possible clinical impact that this may have. Taking into account the ongoing expansion in clinical practice of the use of BAs is a mandatory effort for both researchers and clinicians, as well as an interaction with each other.

Funding

This paper was not funded

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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90. Figure Legend

91. Fig. 1

92. Immuno-tolerant mechanisms and immunogenicity of therapeutical mAbs. Self (as Tregitopes) and “foreign” epitopes usually expand nTreg and aTreg cells. Drug-specific T cell clones are expanded generating central and effector memory T cells. Parallel B cell activation (via a T-dependent or independent pathways) can generate ADA; some T-cell derived cytokines (IL-4, IL-13, IL-10, etc) are responsible for the IgG1/IgG4 subclasses- and IgE isotype switch.

93. Fig.2

94. Tolerance to BAs operating during the first course of therapy is transient and slower to be elicited by the drug than memory T effector cells after a period of lack of antigen stimulation

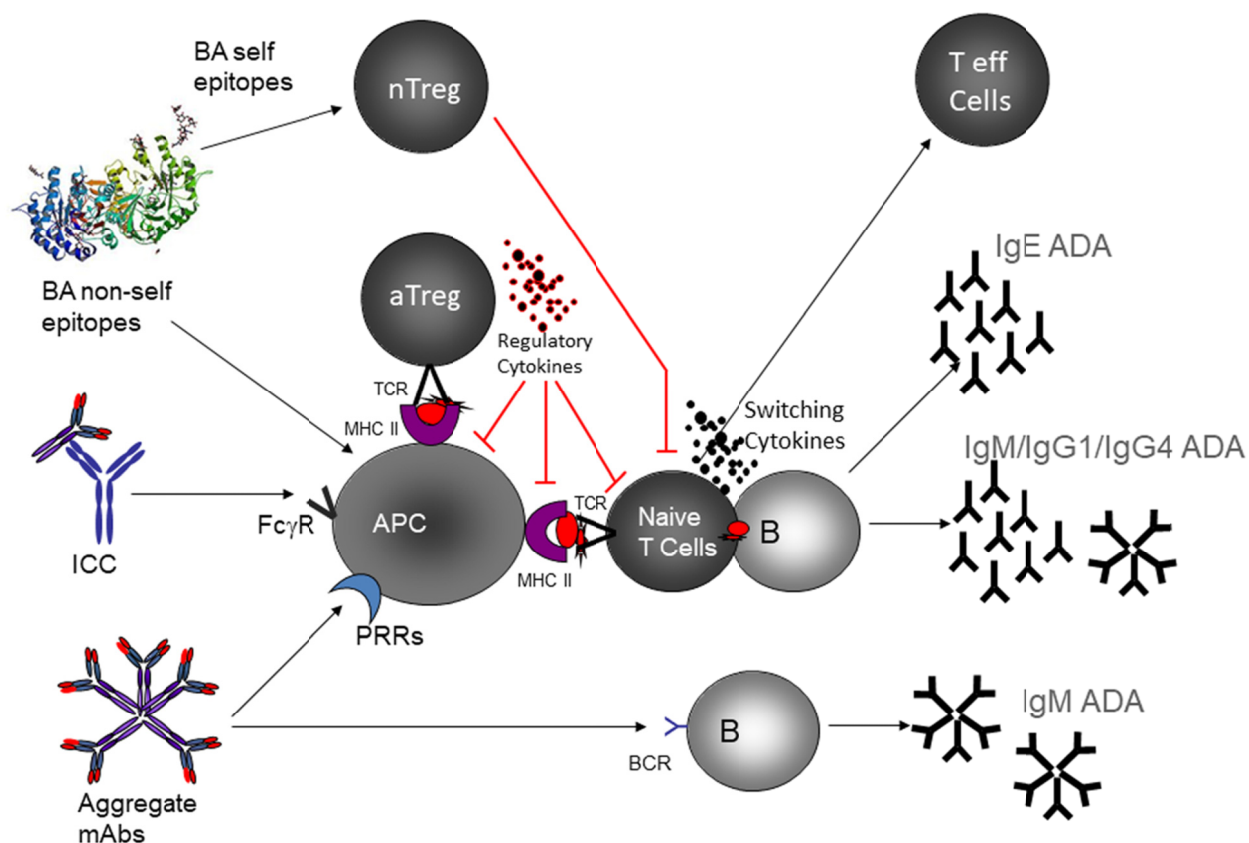


Figure 1

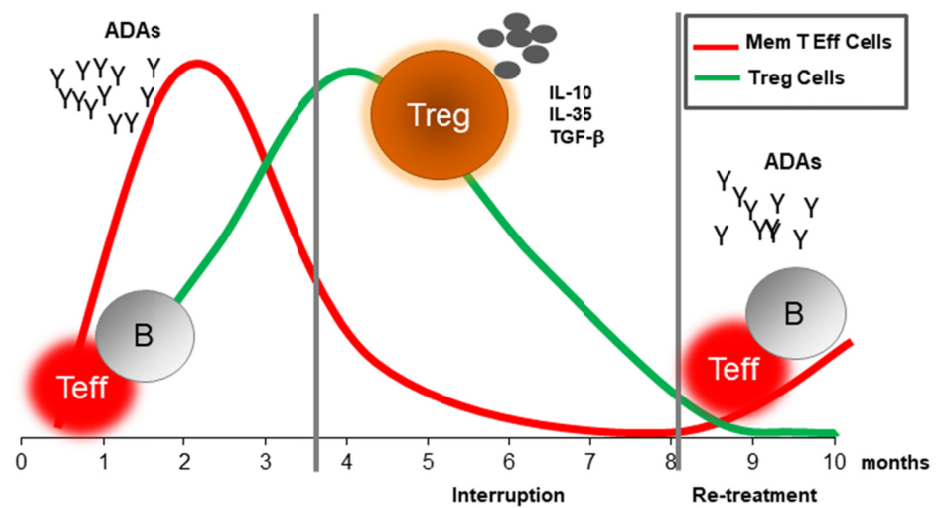


Figure 2