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A Modern View of the Pathogenesis of Allergy with Drug Etiology

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Abstract

Nowadays many diseases are associated with a high risk of drug allergy, and this risk can vary greatly depending on the type of disease. With the progression of disease in HIV-infected patients is increased IgE and decreased the number of CD4+ T-cells. In this case violated the ratio of interferon-gamma-producing (Th1 type) clones of CD4+ T-cells and IL-4 - producing (Th2 type) clones of CD4+ T-cells. In HIV-infected patients, there is the high risk of developing allergies in the form of skin rashes and temperature, and severe skin syndromes Stevens-Jones (SJS) and toxic epidermal necrolysis (TEN) in 6%-10% of cases. CD4+ T cells secrete cytokines, for instance Interleukin (IL-5), Gransim and Eotaxin involve eosinophils to be grown and differentiated. Studies on the antigenicity of antibiotics demonstrated the potential relevance of both categories of drug allergy: hapten and p-i models. In patients with allergic reaction to piperacillin, this medication acts as the hapten, with the formation of the immunogenic conjugate piperacillin - albumin, which stimulates the drug-responsive T-cells. Immunogenetic factors have been identified as risk indicators for the development of hypersensitivity reactions to the representatives of many classes of drugs, such as Abacavir and Nevirapine, Carbamazepine and Allopurinol, etc. Thus, considering the huge genetic polymorphism in systems of drug metabolism in the body and in the systems contributing immune response to the resulting products of conjugation of hapten-protein, evident is the need to further study the role of these systems in the occurrence of adverse reactions to drug therapy, in particular, in the development of allergic complications.

Keywords: Drug, Allergy, HIV, Antibiotics, HLA system, Hypersensitivity.

Contents

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1. Introduction

Some diseases are associated with a high risk of drug allergy, and this risk can vary greatly depending on the type of disease. For example, every third patient with a clinical picture of cystic fibrosis observed the adverse reaction to the antibiotics [1] and the risk of adverse reactions to sulfamethoxazole 10 times higher in patients with HIV than in the general population, and it is more likely manifested in the stage of uncontrolled replication of the HIV virus [2]. The risk of severe skin syndrome Stevens-Jones (SJS) and Toxic epidermal necrolysis (TEN) as an alternative adverse reaction to medicinal substances that was higher in individuals with HIV, cancer, post-transplant disease or systemic lupus erythematous compared with the general population [3, 4]. It is interesting to note that all these diseases in varying degrees, accompanied by changes in the immune system. Nevertheless, at the same time, yet it remains unclear to what extent this increased risk depends on factors associated with diseases or higher exposure to medication [5].

As is known in the basis of the development of allergies, including drugs are immunological mechanisms [6, 7]. Therefore, the initial condition of the immune system depends largely on the likelihood of occurrence and development of allergies. If allergic reactions are immunologic mechanisms, in the context of immunodeficiency will develop immune-inflammatory response and to what extent?

2. Immunological Aspect

It is known that with the progression of disease in HIV-infected patients is increased IgE and decreased the number of CD4+ T-cells. In this case violated the ratio of interferon-gamma-producing (Th1 type) clones of CD4+ T-cells and IL-4 - producing (Th2 type) clones of CD4+ T-cells [8, 9]. Indeed, immunochemical and immunofluorescence studies of biopsy specimens of the skin of HIV-infected patients with skin reactions showed infiltration of activated CD8+ lymphocytes and epidermal production of cytokines [10]. The number of allergic skin reactions in HIV is increasing in comparison with the rest of the population, to a sharp deterioration of the immune system and reduce the number of CD4+ T-cells [11]. Thus, in HIV-infected patients, there is the risk of developing allergies in the form of skin rashes and temperature, and severe skin syndromes Stevens-Jones (SJS) and toxic epidermal necrolysis (TEN) in 6%-10% of cases [12-15]. Thus, the risk of significantly higher in those patients who have CD4+ cell counts above 400 cells/mm^3 and 250 cells/mm^3, respectively for men and women. For example, the number of CD4+ T-cells was a risk factor for hypersensitivity to nevirapine, because in these patients the average value of this indicator was higher (294 vs. 174 cells/мл3) [16].

Such cyclicity and differences in hypersensitivity to the medication immunological nature can be for various reasons.

According to the existing hypothesis in the mechanisms of development of allergy, medicines is hapten dependent and independent ways of presentation of drugs *in vivo* [17, 18]. According to the first way, drugs become immunogenic through metabolism to reactive metabolites, which can bind covalently to proteins or Heptene [19]. Then they are presented via molecules of the human leukocyte antigen (HLA) to T cells. Other – hapten independent path is considered when the drug can directly activate T-cells through interaction with MHC-peptide / T-cell receptor. Then stimulated T cells infiltrating into the skin. CD4+ T cells secrete cytokines such as Interleukin (IL-5), Gransim and Eotaxin that involve eosinophils in the growth and differentiation. Stimulated T cells can also kill autologous target cells through partrimony way, while CD8+ T–cells can also be involved in the allergic process [20, 21].

3. Antibiotics and Allergy

Studies on the antigenicity of antibiotics demonstrated the potential relevance of both categories of drug allergy: hapten and p-i models. For example, in patients with allergic reaction to piperacillin, this medication acts as the hapten, with the formation of the immunogenic conjugate piperacillin - albumin, which stimulates the drug-responsive T-cells [22, 23]. When sulfamethoxazole allergies, as a hapten and p-i hypotheses is potentially important. In patients with such allergies, the proliferation of lymphocytes can be induced by metabolites nitroso-sulfamethoxazole, which covalently bind to non-HLA proteins (hapten) and/or the primary drug or metabolites directly related and reversible with HLA [24-26].

The study also showed that sulfamethoxazole can interact directly with the second further defined region Vb20-1 TCR, which is modified by linking the ability of the TCR to the peptide -MHC complex [27-32].

In the study of Flucloxacillin - induced liver damage, some revealed for the presentation of this drug via the hapten mechanism with multiple HLA types, but also with the presence of the presentation via proteasome-dependent and labile method, limited HLA-B*57:01, result wise direct activation of CD81 T-cells and incorporates p-i mechanism, ending in liver damage [33]. However, others found that activation of CD81 T - cells was restricted to HLA-B*57:01 and is closely linked to HLA-B*58:01, and that activation was dependent and correlated with communication of Flucloxacillin with albumin [34].

In the study of adverse reactions to Nevirapine, the Association of HLA class I were found in relation to serious skin manifestations in many populations, although HLA class II was associated with liver manifestations mainly in the European race, which suggests about the various arrangements of presentation in the manifestation of a variety of immunologically mediated adverse reactions.

4. Viral Infection and Allergy

It is known that viral infections are significant risk factors for the development of hypersensitivity reactions. These reactions can manifest as any type of hypersensitivity, which is based on stimulation of T-cells by viruses (HIV, herpes, Epstein-Barr, cytomegalovirus). Immune responses to the virus may predispose to HLA-associated drug allergy, which can occur because of cross-reactivity of peptide-specific T-memory cells that carry these αβ T-cell receptors that recognize the peptides [35].

However, some data suggest that viruses can also play an independent role in the development of drug allergy, HLA unlimited. This is probably due to reactivation of virus is stopped due to drug-induced T-cell activation, which, in consequence, contribute to the development of the same symptoms as the syndrome of hypersensitivity to the drug rash with eosinophilia and systemic signs of defeat [24]. Therefore, Epstein-Barr virus (EBV) infection is considered the prototype costimulation exanthema associated with receiving the aminopenicillins. Thus, a number of authors [36] found evidence of reactivation of EBV or the human herpes virus 6 or 7 in 76% of patients with DRESS because of their blood, liver, skin and lungs were isolated increased number of CD81 T-cells, which has 3 areas in the sequence of the b-chain TCR, homologous to EBV-specific TCR on CD8. On this basis, it was suggested that the drugs stimulated the reactivation of virus is stopped, which caused virus-driven selection of CD81 T-cells, which led to organ damage. However, it could be a manifestation of cross-reactive memory response of T-cells in the absence of reactivation, which is also enough to cause damage to organs.

Genetic studies on hypersensitivity to medicines have focused mainly on the HLA alleles of the MHC, located on the short arm of chromosome 6 because this area of the genome is considered extremely polymorphic and is associated with the development of both autoimmune and infectious diseases. At the present time known at least 24 ADR associated with different HLA alleles. This, of course, single-nucleotide polymorphisms (SNP) of genes of the HLA system and define the main diversity of individual differences in this process.

5. Immune Reaction

Immunogenetic factors have been identified as risk indicators for the development of hypersensitivity reactions to the representatives of many classes of drugs, such as Abacavir and Nevirapine Mallal, et al. [37] Carbamazepine [38, 39] and Allopurinol [40] etc.

So, in recent years become a well-known fact about the hypersensitivity reaction to Abacavir is closely associated with the allele HLA-B*5701 first class of big histocompatibility complex [41] and the involvement of T cells. Due to the fact that Abacavir without genotyping (as the first-line drug of antiretroviral therapy) is now considered to be the cheapest and most cost-effective option for the treatment of HIV, testing for HLA-B*5701 becomes known and cost-effective pharmacogenetic marker to detect Abacavir-induced hypersensitivity. Therefore, the frequency of detection of HLA-B*5701, the mortality rate from Abacavir-induced hypersensitivity and costs of genotyping are seen as major factors influencing economic efficiency [42].

The clinical usefulness of genotyping the HLA-B*5701 has been validated in large, randomized, double blind, international, multi-ethnic prospective study. Thus, HIV-infected patients with positive HLA - B*5701 genotype were excluded from Abacavir (prospectively screened group), and HIV-infected patients without HLA-B*5701 genotyping was receiving Abacavir (control group). Prospective HLA-B*5701 screening eliminated immunologically confirmed hypersensitivity with a negative predictive value of 100% and significantly reduced the rate of clinically suspected hypersensitivity reactions from 7.8% to 3.4% [43]. Later, some authors demonstrated a strong Association between Abacavir and haplotype including HLA B*5701, HLA-DR7 and HLA-DQ3 genotypes [37]. Regarding Nevirapine of identified HLA-DRB1*01:01 [44] HLA-C*04 [45-47] HLA-C*08 [48] and HLA-B*3505 [47, 49] as risk alleles. In addition, additional HLA alleles (HLA-cw8/HLA-B14) were associated with Nevirapine hepatotoxicity in HIV-infected patients [49, 50]. On the other hand, ABCB1 (MDR1) 3435C > T SNP caused a decrease in the risk of Nevirapine-associated hepatotoxicity in multi-ethnic South African and American individuals [51, 52]. Carriage of the alleles of class II HLA-DRB1*0101 is associated with Nevirapine - associated hepatotoxicity and hypersensitivity (but not with isolated rash) in HIV-infected Western Australians, especially those who have CD4 cell counts lower than 25% [53]. A similar Association with cutaneous hypersensitivity was also reported for Nevirapine and Efavirenz in patients in France, regardless of CD4 values [17].

Carbamazepine - induced SJS/TEN showed the strongest Association with HLA-B*15:02 in some Asian countries: China, Thailand, Malaysia and India [54, 55] but not in Europeans [56] and Japanese [57]. For other types of serious cutaneous ADR caused by carbamazepine the Chinese [58] and to respond to the drug with eosinophilia and systemic syndrome SJS/TEN in Europeans [39] and Japanese [59] a predisposing factor was HLA-A*31:01.

It is also shown that carbamazepine - hypersensitive patients revealed the activation of both HLA-A*31:01 restrictively, carbamazepine - specific CD81 T-cells, and HLA-DRB1*04:04 restriction, carbamazepine - specific CD41 T-cells, indicating that cooperation between the various subsets of T-cells within the extended genetic haplotypes may play a substantial role in the clinical manifestations [59, 60].

Along with this, it is revealed that even for a number of drugs acting via similar ways, clinical manifestations of allergic reactions to medications can vary. For example, abacavir, carbamazepine, and allopurinol produce their effects through the T-lymphocytes that interact with a combination of drugs and specific HLA molecules. However, carbamazepine and allopurinol can cause the development of SJS/TEN whereas abacavir causes a unique clinical syndrome, including SJS/TEN. In addition, variability in the start time caused by drug allergic reactions between 2 days and 3 weeks after initiation of the drugs cannot be explained only by the relationship with MHC. Apparently there are other genetic factors, in certain conditions becomes important, which can determine the ability to develop these reactions in individuals possessing the HLA risk alleles.

Some studies have shown that polymorphism of genes regulating cytokine products can affect the immune response [61]. Interleukin-10 is an anti – inflammatory cytokine secreted by various cells of the immune system, including T lymphocytes, macrophages, dendritic cells, and monocytes. This cytokine has an immunoregulatory effect, such as inhibition of pro-inflammatory cytokines IL-1, IL-6, IL-12, IL-18, and TNF-α, as well as co-stimulatory molecules on antigen-presenting cells. Single nucleotide polymorphisms at positions -1082 (A/G), -819 (T/C), -592 (G/A) proximal promoter region of the gene IL-10 may influence the *in vitro* production of the cytokine. The presence of an allele at position -1082 is associated with low production of IL-10 and occurs regardless of polymorphisms in other positions. During HIV infection, AA was detected in 62% of allergic patients, while GG and GA – in 69% of patients without allergies. Moreover, it was found that the polymorphism of interleukin -10 in position -1082 (A/G) is directly related to the development of allergic reactions to efavirenz [62].

Because the metabolism of most drugs is via the cytochrome P-450 – it is considered one of the major determinants of the pharmacological efficiency and the development of toxic and adverse reactions of drugs, of course with significant individual characteristics [63-68].

So it is known that Nevirapine is metabolized mainly to 8-hydroxypurine with CYP2B6 and to a lesser extent CYP3A4 [68]. CYP2B6 is characterized by a large inter-individual variability in expression and activity in the liver [69]. One of the specific variants of exon 4 (c.516G.T), encoding non-synonymous amino acid position (p.G172H) (rs3745274) (CYP2B6*6/9), associated with loss of function [31, 68-70]. Studies have shown that the variant T-allele associated with higher plasma concentration of the drug, it was associated with Nevirapine-induced cutaneous reaction, which was stronger with a combination of the genotype CYP2B6 516G T carriers with HLA-Cw*04 alleles [47, 71-75]. Identification of polymorphisms CYP2B6 516G > T, 983T > C, 785A > G and 21563C > T SNPs are associated with increased plasma concentrations of Efavirenz and the development of more severe CNS lesions in HIV-infected, as well as increased concentration of Efavirenz was associated with CYP2A6 -48T > G and homozygous GG for UGT2B7 735, SNP microsomal enzyme uridine 5–diphospho-glucuronosyl transferase (UGT) [76-79]. Regarding phenytoin, clinical supervision among Taiwanese, Japanese and Malaysian patients showed a strong Association with the allelic variant CYP2C9*3, which was associated with decreased activity of CYP2C9 by 90% [80]. Because phenytoin has a narrow therapeutic index, lower the activity of the allelic variant CYP2C9*3 reduces the metabolic clearance and increase plasma concentrations, which is consistent with clinical observations a dose-dependent relationship in the risk of cutaneous manifestations.

This also implies that the relative disadvantage, in the same way, metabolism does not necessarily predispose to the development of serious ADR, if the ground clearance of this drug is involved in numerous metabolic pathways.

It should be noted that the main problem of the research Association of the SNP phenotypes is the lack of reproducibility [81]. This could be due to the relatively small size genotyping of the population, lack of statistical power of the analysis or offset selection [82]. In addition, SNP Association observed effect is found only within specific ethnic groups, but not in others. Also, some positive Association, likely to have been obtained after numerous statistical comparisons, which gives place to a potentially random Association caused by changes. Moreover, usually reported only positive results, meaning that some of the published associations could not be openly refuted by other authors who failed to find such relationships. On the other hand, the Association of SNP-phenotype could not be necessarily associated with functional effects of gene variants, but perhaps the presence of another variant on the same chromosome in a non-equilibrium context, the combination of which is called a haplotype.

Finally, most pharmacogenetic studies are retrospective or cross, so it would be more informative to conduct large and progressive research in multiethnic populations, with the simultaneous genotyping of many SNPS, known as relevant in the general population [81, 82].

However found that the use of SNP-genotyping in relation to the alleles HLA-B*5701 to prevent Abacavir - associated hypersensitivity reaction is economically advantageous diagnostic tool, for which managed to bring the negative predictive value to 100% for all ethnic groups [83].

Considering this, it became clear that for primary prevention of allergic drug reactions are necessary to develop an accurate, rapid, inexpensive, and easily interpreted laboratory tests to meet the following prerequisites:

- To have at least an acceptable safe profile;
- Alternative medications should be absent or be more expensive, or have lower efficacy and/or safe worst profiles;
- An allergic reaction should be sufficiently high to ensure their prevention;
- The frequency of preventable allergic reactions must be relatively high;
- Must have high negative predictive value, and favourable positive predictive value to the number of tests performed, necessary to prevent the allergic reactions were actually enforceable in practice.

6. Conclusion

For further research in the area of disclosure of mechanisms of occurrence and development of drug allergy and its prevention can be extremely important in a number of identified circumstances:

1) Various organ system affected by ADR, and most significantly among them is leather and the liver and muscles (statin – induced autoimmune myopathy and HLA-DRB1*11:01) [84] and neutrophils (clozapine – induced agranulocytosis and HLA-DQB1) [85]. It is determined whether the form of HLA alleles which organ system needs to be affected remains unclear, but probably it can play a role together with other factors, as for example, with a variety of genetic variants, the expression of organ receptors and clonotypic T-cells.

2) The Association sometimes show considerable ethnic variation, reflecting the basis of the distribution of HLA alleles involved. The most impressive example of this can be considered the Association of HLA-B*15:02 with carbamazepine - induced syndrome Stevens-Johnson (SJS) and toxic epidermal necrolysis (TEN) among Chinese, Thai, and Malay patients [86] but not among Europeans [38]. The overall prevalence of HLA-B*15:02 ranges from 4% to 15% in these populations, but is manifested in less than 1% of Japanese and Korean persons and is extremely rare in Europeans (<0.01%).

3) The same HLA alleles may be associated with adverse reactions to therapeutically and non-structural components, but with effects in different organs. The best example of this is the Association of HLA-B*57:01 with hypersensitivity to Abacavir Mallal, et al. [87] and with Flucloxacillin-induced hepatotoxicity [88].

4) The same type of organ damage can occur with the same HLA allele, even with therapeutically and structurally unrelated components. For example, HLA-DRB1*15:01 is associated with liver damage as in the appointment lumiracoxib [89] and coamoxiclav [90].

Are there some HLA alleles that predispose to certain forms of organ damage, it will become clear after further research with other medications, but probably it is based on the possibility that certain HLA alleles may be more highly Expression Engine specific organs. Accordingly, recent genome-based studies indicate that HLA-DRB1*15:01 is also associated with alcohol-induced cirrhosis of the liver [91].

5) Although most of the Association correspond to the time interval necessary to induce the immune response (and find a clinical and histological confirmation), for some forms of organ damage HLA Association were amazing, and it was found that the general rules of immune-mediated damage occurring soon after beginning drug administration, are not necessarily correct in all cases. For example, the lumiracoxib-induced liver disease usually occurs after more than 100 days of drug 12, which is not a regular time interval associated with liver damage caused by other drugs (e.g., coamoxiclav). For clozapine – induced agranulocytosis, the reassignment of the drug does not necessarily result in a more rapid recurrence of the reaction [92] contrary to other forms of immune-mediated drug damage, as in hypersensitivity to Abacavir Clay [93].

6) Finally, the drugs most closely associated with cutaneous ADR, (such as penicillin and sulfonamides), are unlikely to have an association with HLA alleles. Perhaps they form multiple epitopes and therefore interact with multiple HLA alleles, but this may not be a sufficient explanation for the formation of the strong Association between Flucloxacillin-induced hepatotoxicity and HLA-B*57:01. A possible explanation for the results of such research can be a mixture of the phenotypes of the studied individuals, poor assessment of causality and inadequate sample sizes. It proved one of the studies, which were carefully phenotyping the required number of patients with penicillin-induced IgE-mediated reaction type 1, revealed the Association within the HLA-DRA region [94].

Thus, considering the huge genetic polymorphism in systems of drug metabolism in the body and in the systems contributing immune response to the resulting products of conjugation of hapten-protein, evident is the need to further study the role of these systems in the occurrence of adverse reactions to drug therapy, in particular, in the development of allergic complications. The elucidation of these questions has not only theoretical importance in understanding the mechanisms of occurrence and development of drug Allergy, as a special form of Allergy, but becomes of particular interest and in practical terms.

7. Consent

It is not applicable.

8. Ethical Approval

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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