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Guidelines for assessing immunocompetency in clinical trials for autoimmune diseases

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Abstract

Clinical trials testing the safety and efficacy of immunosuppressive agents for the treatment of autoimmune diseases should also be designed to evaluate immunocompetency. The most clinically relevant outcome for assessing immunocompetency is the infection rate. Therefore, a systematic approach to screening, monitoring, and reporting infections, modeled after the recommendations of the American Society of Transplantation, is presented. However, because the baseline infection rate in most autoimmune diseases is low, additional tests for immunocompetency should be considered. Evaluation of vaccine responses, an alternative clinically relevant approach, may be particularly useful. Other adjunctive approaches to evaluation of immunocompetency are discussed including immunization with non-vaccine neoantigens, surveillance of chronic viral infections, in vivo or in vitro assessment of cellular immunity, and analysis of innate immunity. Banking genetic material to allow genotyping should be considered particularly if a central repository for samples from different trials can be established.

Keywords

Immunocompetency; Immunosuppression; Autoimmunity; Immunization; Clinical trials; Guidelines

Introduction

Infections are the most common life-threatening complications of treating autoimmune disease. As with transplant patients the frequency, severity and type of infections depend on the degree of immune suppression, the intensity of exposure to potential pathogens, pre-existing immunity, and in some cases the unique properties of the immunosuppressive drug [1]. A second problem with chronic immunosuppression is the increased rate of

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malignancies. With post-transplant lymphoproliferative disease (PTLD) the relationship between malignancy and immunosuppression is quite clear, but there is now increasing concern that immunosuppression may play a role in other cancers as well [2,3]. As novel immunosuppressive drugs are tested in clinical trials, the systematic evaluation of the risk of infectious and malignant complications will be critical. The following report by the ACE immunocompetency committee evaluates different approach and provides recommendations for standardized assessment of immunocompetency in clinical trials of immunosuppressive agents for autoimmune disease.

Infections in autoimmune diseases

An increased rate of infections is the gold standard for determining whether a patient is immunocompromised. To help standardize evaluation of infectious complications American Society of Transplantation (AST) has recently published guidelines for clinical trials of immune suppression for organ transplantation [4]. Criteria for probable and definite infections with various types of agents as well as a reasonable approach to screening and surveillance are provided. The ACE immunocompetency committee has recommended a systematic approach to screening, monitoring, and reporting infectious complications and malignancies in clinical trials of immunosuppression for autoimmune disease based on the AST guidelines (see Table 1). It is strongly recommended that investigators involved in trials for autoimmune diseases read carefully and follow the AST guidelines. Adopting this standardized approach will allow comparison between trials and facilitate meta-analysis.

Although the rate of infections can be high in certain autoimmune diseases such as necrotizing vasculitis, inflammatory myositis, and severe SLE, in the vast majority of patients with autoimmune diseases, rates of infections are fairly low. For example, in patients with rheumatoid arthritis (RA) infections are relatively infrequent, e.g., averaging 3 serious infectious events per 100 patient years in randomized clinical trials of anti-TNF agents [5–13]. A similar rate of serious infections has also been found in a recent German observational cohort of patients on biologics; the rate of serious infection was 2.3 per 100 patient years for patients not on anti-TNFs with the risk approximately doubling for patients on anti-TNFs [14]. Opportunistic infections are relatively uncommon in patients with RA, and severe opportunistic infections are rare in the setting of clinical trials, e.g., the risk of opportunistic infection with adalimumab has been reported to be 0.075 cases per 100 patient years. (See adalimumab package insert.) However, because rheumatoid arthritis is one of the most prevalent auto-immune diseases, affecting about approximately 2 million patients in the U.S.A., even a small increase in the rate of serious infections would have major impact, e.g., a doubling of the infectious rate could translate in 60,000 serious infections a year.

The group size needed to detect a doubling or tripling of infections based on the rate of infections in the control group is shown in Table 2. Based on this power analysis detecting a change in the rate of infections will not be feasible in individual trials of most new drugs for autoimmune diseases. With low rates of infection even a substantial sized trial may fail to pick up increased rates of infection or malignancies. As recently demonstrated with anti-TNF therapies, meta-analysis combining the results of multiple trials can provide sufficient power to detect increased rates of both serious infections and malignancies [3].

Although rates of infection are certain to remain the gold standard for immunocompetency, alternative approaches for assessing immunocompetency should be considered. The merits and problems with several of these alternative approaches are discussed below.

Immunization

Therapeutic vaccines for common respiratory infections such as influenza and pneumococcus are an important part of health maintenance, and the use of these vaccines in patients with chronic rheumatologic disease is strongly recommended [15]. Antibody responses to therapeutic vaccines are important, but imperfect, biomarkers for protection from infections.

Influenza and pneumococcal vaccine prevent disease in approximately 80% of healthy subjects [16–18]. Given the frequency of these infections and the large and increasing number of autoimmune patients who are mildly or moderately immunosuppressed, the immune response to influenza and pneumococcal vaccines in these patients is of considerable clinical importance. An additional reason for determining whether patients respond to influenza and pneumococcal vaccines is that there are alternative approaches that may be able to provide protection. For example, even if the immune response to pneumococcal polysaccharide vaccine is poor, then the currently available conjugate vaccine might still be effective [19]. Likewise chemoprophylaxis during the yearly influenza epidemic is the current Center for Disease Control recommendation for patients not expected to respond to flu immunization [18]. Moreover, it may be possible to use adjuvants to boost the response to influenza vaccines. The use of adjuvants in immunosuppressed patients as an alternative to standard influenza immunization may be especially important due to the threat of pandemic influenza [20,21].

Although influenza and pneumococcal vaccines are of great clinical importance for immunocompromised patients, deciding how to use these vaccines to determine immune competency is not trivial. For example, the response to influenza immunization is dependent on the year of the study and the strains in the vaccine, dose, age, sex, prior immunization, and pre-vaccination antibody titer. The response to pneumococcal polysaccharide is similarly influenced by age and pre-existing antibody titer. Moreover, there is debate about the best assay for anti-pneumococcal antibodies, i.e., the assay that correlates best with protection may be an opsonophagocytic assay rather than the presently used ELISA [22]. In addition, both of these vaccines have multiple components. For all these reasons, the definition of a “good” response can be complicated. A 4 fold increase from baseline is probably a reasonable criterion for a significant immune response, while achieving a “protective” titer at a rate similar to healthy controls is probably the best definition of immune competency. Although randomized, placebo-controlled trials are the only way to determine the true extent of immune suppression, non-randomized studies may be useful in determining which proportion of patients on a new therapy fail to achieve protection after immunization.

Secondary immune responses to tetanus and diphtheria toxoids are robust in healthy individuals, and responses are easily measured by ELISA. In general the response to tetanus

is better than the response to diphtheria with the dT vaccine given to adults. Thus, measuring both antibody responses provides assessment of a strong and a moderate stimulus for antibody responses.

Primary immune responses are generally more susceptible to immune suppression than secondary immune responses. Therefore, in some situations immunodeficiency may only be detected in response to primary immunization. Evaluation of responses to primary immunization may be especially important with drugs that interfere with co-stimulation since primary responses are more dependent on these pathways than secondary responses. Response to primary immunization can be tested in some individuals with therapeutic vaccines such as hepatitis A and B vaccines or in all individuals with non-vaccine immunogens such as KLH or $\Phi\times 174$. DTH and in vitro cellular responses to KLH can also be used to assess the effects of immunosuppressive agents.

The use of immunization for assessment of immune suppression is illustrated by two new drugs, abatacept and rituximab, that have just received FDA approval for use in patients with rheumatoid arthritis who have failed anti-TNF therapy. Both of these drugs have been shown to block humoral responses to immunization. Abatacept at the dose approved for RA has a profound effect on the response to KLH and $\Phi\times 174$ [23], and rituximab has been shown to block the primary response to $\Phi\times 174$ and the secondary response to tetanus [24,25]. The effects of these drugs on response to influenza and pneumococcal vaccines have so far not been tested and will be of great interest and importance. Designing immunization studies will be relatively easy for abatacept since it is given on a regular basis as a maintenance drug. On the other hand, rituximab is given intermittently and causes a profound depletion of memory and naive B cells for many months therefore designing immunization studies will be problematic. The time to recovery of B cells and the subsets of B cells that return varies dramatically; thus, exactly what is being tested will be very dependent on the degree and type of B cell recovery at the time of immunization.

Using immunization to determine immune competency has several advantages. First, immunization measures in vivo responsiveness, and therefore *prima fascia* is more valid than in vitro assays. Second, since every subject has an outcome that can be measured immunization provides an excellent power to discriminate groups. For examples of the number needed per group to provide 80% power for discriminating HIV patients from controls using a variety of immunization, see Table 3. Immune responses in HIV patients have been relatively well studied with a variety of vaccines. For the number needed to treat to detect a difference between patients treated with abatacept vs. placebo, see Table 4. The study was perhaps the best example of a well done study evaluating the effect of a novel immunosuppressive drug on primary immune responses. The major downside to immunization is that any given vaccine can really only be used once and therefore can provide information on immune responses at only one time period.

Surveillance of viral infections

Herpes virus infections have been a major problem with transplant patients. Reactivation of latent infections can occur and primary infections can be severe. EBV and CMV are major

clinical problems especially with aggressive immune suppression that targets T cells. Post-transplant lymphoproliferative disease and other EBV-related malignancies are also concerns with immune suppression. Thus, EBV and CMV DNA viral titers are frequently followed after transplantation. Indeed, screening, prophylactic anti-virals, surveillance for reactivation or primary infections, and treatment for EBV and CMV disease are always part of standard protocols in transplantation. Autoimmune patients treated with high dose immune suppression may have clinically significant EBV and CMV infections as well as a host of other opportunistic and non-opportunistic infections. Moreover, therapies that target T cells, e.g., anti-CD3 monoclonal antibodies, may cause EBV viral reactivation, fever and flu like symptoms even when general immunosuppression is not severe and most other infections are avoided [26]. To complicate matters, increased EBV viral load has been reported in most patients with active RA or SLE [27,28]. There is even some evidence that methotrexate may directly affect expression of EBV mRNA in latently infected cells and methotrexate has been associated with EBV-associated lymphoproliferative disease [29]. Thus, as new immunosuppressive agents are introduced into the treatment of autoimmune disease some thought needs to be given to managing the effects of immune suppression on EBV and CMV.

Other chronic viral infections such as hepatitis B and C may also need to be taken into account. Patients with these infections are often excluded from trials but monitoring infection will be necessary if they are included. The JC virus, a widespread polyoma virus that causes progressive multifocal leukoencephalopathy (PML), may become activated in severely immunosuppressed patients. Unfortunately, the JC virus was also found to be reactivated and to cause PML in patients with multiple sclerosis treated with natalizumab, a monoclonal antibody against the $\alpha 4$ chain of integrins [30–33]. The implications of this generally unanticipated complication are still unclear but the merits of monitoring JC virus should be discussed in trials of immunosuppression. Papilloma virus infections are of concern in immunocompromised patients including immuno-suppressed transplant patients and SLE patients [34–37]. Keeping up to date with Pap smear should be strongly encouraged and for trials with aggressive immunosuppression there should be consideration for requiring Pap smears. In any case data on the occurrence and results of Pap smears should be collected.

Analysis of cellular immunity

The delayed type hypersensitivity (DTH) skin test reaction was discovered in the 19th Century by Robert Koch and has been used to assess immunocompetency. DTH skin tests with microbial antigens have the advantages of being antigen-specific, relatively simple, and an in vivo assay. A standardized antigen for *Candida albicans* DTH testing is available (Candin[®], AllerMed Laboratories, Inc. San Diego). The standardized Mumps Skin Test Antigen for DTH skin testing is not currently available. DTH skin testing is still of interest for assessment of immunocompetency but is relatively insensitive and difficult to quantify. Fortunately, a host of new techniques have been developed and show considerable promise. However, many have not been applied to assessment of immunocompetency and still need to be validated.

With the advent of HIV infections enumeration of lymphocyte subsets by flow cytometry has become the most widely used tool for assessment of cellular immunity. The association of CD4 lymphopenia with opportunistic infections has also been reported in autoimmune patients not on immunosuppressive drugs and with idiopathic CD4 lymphopenia [38,39]. There are also a few reports suggesting that CD4 T cell levels may also be useful in assessing risk of infection in patients on immunosuppressive therapy for autoimmune disease [40]. Unfortunately, many immunosuppressive drugs do not cause CD4 lymphopenia, and conversely there are reports of severe CD4 lymphopenia after treatment with CAMPATH and relatively little effect on infections [41]. Differentiation of additional T cell subsets may improve the usefulness of flow cytometry for determining immune competency [42]. T cell subset analysis may be especially helpful if used in conjunction with MHC/peptide tetramers to enumerate antigen-specific T cells [43,44], or functional assessment using whole blood stimulation with antigen as described below.

Functional assessment of lymphocytes is another promising approach for evaluating immunocompetency. As mentioned before there is an FDA approved assay for immune suppression in transplant patients [45]. This whole blood assay measures CD4 T cell stimulation by the mitogen phytohemagglutinin (PHA). An advantage of whole blood assays is that immunosuppressive agents present in blood are not washed out during the isolation procedure—a critical point when assessing immune suppression rather than immunodeficiency. Functional assays for specific immunity to some of the infections likely to cause problems, e.g., EBV, CMV, or VZV, or tuberculosis have also shown some promise but are still in development. For example, there is an FDA approved in vitro assay for immunity to tuberculosis [46]. This assay has been used to detect latent tuberculosis in immunocompromised and immunosuppressed patients, but has not been used to follow the effects of immune suppression on anti-TB responses [47]. Interestingly, a whole blood in vitro assay has been used to show that in some patients stimulation by mycobacterial antigens decreases dramatically after starting anti-TNF therapy [48]. The response of CD4 T cell to CMV in transplant patients has been studied using stimulation in whole blood followed by flow cytometry. This assay does appear to correlate with infectious episodes ($r = -0.57$, $p < 0.005$) [49]. Similar assays can be used with a variety of antigens to characterize the response in lymphocyte subsets [50]. Assessment of antigen-specific immune responses with in vitro assays using isolated cell populations can also be used to study differences in cytokine secretion that define functional lymphocyte subsets and may be used to assess immunomodulation by immunosuppressive agents [51]. A major advantage of flow cytometry and in vitro functional assays for cellular immunity is that they can be repeated over time. Therefore, they can be used to follow the effects of immunosuppressive drugs and may potentially be used to modify dosing based on the degree of immune suppression. Of course, evaluating the effects of immunosuppressive drugs on immunocompetency must take into account the effects of systemic autoimmunity on these functional assays. In particular, in SLE T cell signaling via the T cell antigen receptor and production of IL-2 may be deficient because of disease rather than immunosuppressive medications [52–54].

In conclusion, there are some very promising assays for assessing cellular immunity in immunosuppressed patients, but the clinical significance of these assays both in terms of

suppressing harmful immune responses and in terms of risk of infections remains to be validated. Moreover, currently these assays are labor intensive and are not standardized.

Innate immunity

Many of the drugs currently used to treat autoimmune disease have a direct effect on innate immunity. For example, the effect of glucocorticoids on activation of leukocytes has been well documented [55]. In addition methotrexate has been shown to decrease leukocyte activation by increasing the production of adenosine and anti-malarials have been shown to block activation of dendritic cells and B cells via toll-like receptors [56,57]. Analyzing the number and function of leukocyte especially may be a very direct approach for assessing the effects of certain immunosuppressive agents. The best assays to use will depend on the drugs mechanism of action. Further work in this area would be of interest.

Genetic polymorphisms

Genetic polymorphisms can influence susceptibility to infection. Clinical importance of genetic variation has been demonstrated with complement proteins, Fc γ receptors, cytokines, toll-like receptors, and other components of the innate immune systems [58–61]. Genetic polymorphisms in innate immunity are likely to be important in determining the risk of infection in immunosuppressed autoimmune patients, especially since defects in innate immunity are risk factors for some autoimmune diseases such as lupus [62,63]. The development of gene chips that can analyze genetic polymorphisms provides the opportunity to study the effect of these polymorphisms on the risk of infection in immunosuppressed patients. The best strategy for studying the genetics of infection risk in immunosuppressed patients remains to be determined. However, large numbers of patients and concomitant analysis of acquired immunity to specific infections may be required. Thus, studies to determine the role of genetic polymorphism in susceptibility to infection will be outside the scope of most clinical trials. Collecting information and genetic material from a large number of trials may allow this type of analysis and should be investigated.

Summary

The current report was undertaken to encourage a systematic evaluation of immune competency in ACE trial of immunosuppressive agents for autoimmune diseases. A major conclusion is that any real progress will require pooling information from multiple trials. To do this well and to develop new approaches, multiple government and non-government entities will need to be engaged. Such a task is well beyond the scope of the ACE. Nevertheless, it is hoped that this report will help provide momentum for a broader discussion.

ACE recommendations for assessing immunocompetency in clinical trials for autoimmune disease:

- #1** Standardized screening, monitoring, and reporting. The AST recommendations should serve as guidelines for recognizing and reporting infections in clinical trials of immunosuppression for autoimmune diseases [4]. The rates of

infections and malignancy determined with standardized protocols should be considered the gold standard for immunocompetency and an important safeguard to adequately documented infectious complications. However, most trials of immunosuppressive agents should have relatively low rates of infection and even lower rates of malignancy, and therefore be insufficiently powered to detect even a two fold increase. Collection of safety data from multiple trials and meta-analysis of the combined results should be an essential part of product development.

- #2** Immunization. One major advantage of therapeutic vaccines is that induction of protective antibody levels is a clinically meaningful measure of immunocompetency, and can help determine the need for alternative approaches to prevention. Therefore, evaluation of immune responses to therapeutic vaccines, especially influenza and pneumococcal vaccines, should be a high priority. In the early phases of clinical development of a new drug immunization studies especially with neo-antigens such as KLH or $\Phi\times 174$ may be of interest for demonstrating a drug's immunosuppressive potential. For most new drugs immunization studies using therapeutic vaccines should be considered either in the late stages of clinical development or soon after approval.
- #3** Surveillance of viral infections. Screening and monitoring for EBV and CMV infections should be considered in all trials of immunosuppressive drugs for autoimmune diseases and are strongly recommended for all trials targeting T cells. Discussions on screening and monitoring for JC virus and other unusual infections should also be part of trial protocol development.
- #4** Analysis of cellular immunity. Flow cytometry assays to quantify lymphocyte subsets and antigen-specific assays for T cell function should be a focus for future development. These assays will need to be correlated with rates of infection and with immune responses to immunization to provide a biologically relevant validation. Standardization and centralization of assays for cellular immunity should be given a high priority. Such standardization will also provide an infrastructure and useful controls for autoantigen-specific cellular assays as these assays are developed. While whole blood assays may be important for functional assays of cellular immunity, the reliability and validity of such assays remain to be determined.
- #5** Analysis of innate immunity. Assays for leukocyte activation and function, especially dendritic cell activation and function, would be of interest in determining the effects of immunosuppressive drugs, however there has been insufficient work to assess this approach.
- #6** Evaluation of genetic polymorphisms. The role of genetic polymorphism in toll-like receptors, complement proteins, Fc γ receptors, and other components of innate and acquired immunity in susceptibility to infection should be of considerable interest. Whether or not such genetic studies are feasible in the context of clinical trials is debatable. A repository for collecting genetic material and clinical data over many clinical trials should be considered.

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Table 1

Guidelines for screening, monitoring, and reporting infections in clinical trials for autoimmune diseases
(adapted largely from AST guidelines for organ transplantation [4])

Screening	
1	History <ul style="list-style-type: none"> a. Serious infections — any hospitalizations for infections, any deep space infections, sick days due to infection in the past year b. Frequent or recurrent infections — antimicrobial therapy in the past year, sinusitis, otitis media, bronchitis, pneumonia, urinary tract infections, cellulitis, cold sores or genital Herpes, genital or other warts, shingles c. High risk behavior — i.v. drugs, multiple sexual partners d. Travel to endemic areas and other exposures — developing countries, American Southwest, pet birds e. Immunization — pneumococcal, influenza, diphtheria/tetanus, childhood vaccines, chickenpox, or Varicella vaccine f. Pap smear date and results g. T.b. — past infection, BCG immunization, past skin testing, high risk of past or present exposure
2	Blood tests (baseline sera and DNA/RNA should also be stored) <ul style="list-style-type: none"> a. HIV-1 and HIV-2 b. Hepatitis B and hepatitis C c. Syphilis d. CMV and EBV for studies with T cell immunosuppression e. HTLV-1 and HTLV-2 for at risk populations f. Toxoplasmosis, Herpes simplex 1 and 2, Varicella Zoster virus for studies with severe immunosuppression
3	Tuberculosis — PPD or in vitro assay (QuantiFERON®-TB Gold Test, Cellestis Limited, Carnegie, Victoria, Australia)
Monitoring — serum and DNA/RNA should be collected for any unexplained illness	
1	EBV — PCR with T cell immunosuppression
2	CMV — PCR with T cell immunosuppression
3	Hepatitis C — if patients with prior infection are included, then obtain baseline liver biopsy and genotype virus and monitor liver enzymes and HCV RNA
4	Hepatitis B — if patients with prior infection are included, then consider prophylaxis with lamivudine and monitor liver enzymes and HBsAg (for immune patients) or HBV DNA (for patient with chronic infection)[64]
5	Pap smears should be followed at least yearly
Reporting — results should be expressed as serious or non-serious events per patient year of exposure, and also by organism and syndrome	
1	Viral infections — organism and syndrome <ul style="list-style-type: none"> a. CMV — CMV syndrome, pneumonia, gastrointestinal disease, hepatitis, CNS disease, retinitis, other tissue invasive diseases b. EBV — non-specific viral syndrome, mononucleosis, post-transplant lymphoproliferative disease, lymphoma c. Varicella Zoster — primary infection, Zoster, tissue invasive disease d. Herpes simplex — orolabial or genital/perianal, tissue invasive disease e. Human Herpes virus-6 and-7 — febrile viral syndrome, tissue invasive disease f. Human Herpes virus-8 — Kaposi's sarcoma g. Hepatitis C — reactivation and/or progression of liver disease h. Hepatitis B — reactivation and/or progression of liver disease [64] i. JC polyoma virus — progressive multifocal leukoencephalopathy
2	Fungal infections — organism and site; invasive or colonization

- a. *Candida*, *Cryptococcus*, or other molds
 - b. *Aspergillus* or other mycelial fungi
 - c. Endemic fungal infections — Histoplasma, Blastomyces, Coccidioides, Paracoccidioides
- 3 Mycobacterial infections
 - a. Tuberculosis
 - b. Atypical mycobacteria — invasive or colonization
- 4 Bacterial infections — by syndrome and organism; proven or possible
 - a. Respiratory — rhinitis, pharyngitis, sinusitis, otitis, bronchitis, pneumonia, empyema
 - b. UTI — asymptomatic bacteruria, acute uncomplicated cystitis, acute pyelonephritis, perinephric abscess
 - c. Intra-abdominal infections — abscess, cholangitis, peritonitis
 - d. Soft tissue infections — cellulitis, abscess
 - e. Bacteremia, sepsis
- 5 Malignancies
 - a. Virus-associated malignancies
 - i. PTLD
 - ii. Kaposi's sarcoma
 - iii. Cervical carcinoma
 - iv. Squamous cell carcinoma of the skin
 - b. Lymphomas — histological classification and EBV+/-
 - c. Basal cell carcinomas
 - d. Other malignancies

Table 2

Group size to have an 80% power ($\beta=0.80$) of detecting a significant ($\alpha=0.05$) increase in the rate of serious infections

Rate of infections in control group	Number in each group to detect doubling of infections	Number in each group to detect tripling of infections
1%	2525	866
2%	1240	425
3%	813	278
5%	474	160
10%	219	73
20%	91	28

For Tables 1–3 power calculations were used to estimate the number needed per group for a power of 80% and an $\alpha=0.05$. The number needed per group was based on 2 proportions and was calculated using Russ Lenth's website (<http://www.stat.uiowa.edu/~rlenth/Power/>).

Table 3

Summary of antibody response in controls vs. HIV patients

Immunogen criteria for + response	References	Type of response	Type of controls	Response in controls	Type of HIV	Response in HIV	Number needed per group
Diphtheria (dT) protective	[65]	TD recall	HIV- staff	100%	CD4 >300	73%	34
Tetavalent influenza protective	[66]	TD	HIV- hetero	94, 100, 94, 93%	Seropositive asymptomatic	52, 64, 89, 32%	21, 23, >100, 12
Hepatitis B protective (4 studies reviewed)	[67]	TD neo	HIV-	88, 90, 91, 94%	HIV	43, 33, 56, 53%	21, 14, 30, 22
Hepatitis A protective	[68]	TD neo	Literature normals	>98%	CD4 >500	67%	29
Φx174 normal	[69]	TD neo	Healthy HIV-	>95%	HIV+	36%	12

Antibody response to neoantigens in patients with psoriasis treated with CTLA4Ig or placebo [23]

Table 4

Immunogen Criteria for + response	Type of response	Control group	Response in controls	Treated group	Response in treated	Number needed per group
Φ×174	TD neo	Placebo	>95%	CTLA4Ig	6%	6
Normal 1°				25 mg/kg		
Φ×174	TD neo	Placebo	>95%	CTLA4Ig	0%	5
Normal 2°				25 mg/kg		
KLH	TD neo	Placebo	>95%	CTLA4Ig	56%	23
Normal 2°	Normal			25 mg/kg		