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WHY CAN'T WE FIND A NEW TREATMENT FOR SLE?

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Abstract

No new therapy for systemic lupus erythematosus has been approved. In the last decade, the development of several novel compounds has been pursued for lupus, but so far nothing has been proven to be effective. This review discusses some of the reasons why it may be so difficult to demonstrate that a novel therapy is effective for this disease. These include the complexity of the disease itself; the lack of reliable outcome measures; our limited understanding of the pathogenesis of the disease; the propensity of lupus patients to have bad outcomes and to react to medicines in unusual ways; the heterogeneity of the patient population; the unpredictable course of disease in individual patients; and the lack of reliable biomarkers. Although some of the tested targeted compounds that are apparently based on strong preclinical and mechanistic data may indeed not be effective therapies for SLE, it is hard not to believe that among the various specific agents now being tested that at least some of them should downregulate the abnormal immunoregulation characteristic of SLE, and thus be clinically effective. We need to be persistent and imaginative in identifying these effective agents and proving their efficacy so that they may be widely used in our lupus populations.

Keywords

lupus; therapy; clinical trial; biologic; biomarkers

It is striking that the only medicines approved for use in SLE are aspirin, corticosteroids, and hydroxychloroquine. No new agent has been added in the last 30 years (1)! It is clear to anyone who cares for these patients that the need is great for better therapies, and the outcomes data for lupus renal disease or mortality, while arguably improved compared to earlier, still attest to the failure of our present approaches for many patients (2). In the last ten years, the development of targeted biologicals, and their testing in SLE, have raised hopes considerably; but no randomized control trial (RCT) of a novel therapy has been successful so far. This review will attempt to summarize some of the factors that might have contributed to this ongoing failure, in order to inform our strategies for the near future.

In our discussion, we are considering SLE to be fundamentally a loss of B-cell tolerance (3). This is not meant to imply that B cells are the only or even the most important potential therapeutic target for this disease, since obviously multiple other cell populations and inflammatory pathways must contribute to this loss of B cells tolerance and to the ultimate clinical pathology that is observed. But in terms of our speculations about disease pathogenesis

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and drug development, it is useful to combine the understandings from a number of syndromes or models that have variously been called lupus, even if one could reasonably argue that many of these examples are really quite different from what we term SLE in the clinic or in clinical trials. In the murine studies, many of the genetic manipulations lead to production of autoantibodies characteristic of SLE, such as anti-DNA, but perhaps only very mild clinical pathology such as renal disease (4). In humans, patients with C1q deficiency are classified as having SLE, even though their disease manifestation seem to fit a special category (5). Nevertheless, it appears to us that a unifying theme in SLE is indeed the loss of B cell tolerance to nuclear antigens. Maintenance of this tolerance must involve special immunological regulatory mechanisms that are fundamental to the immune system, and failure of such immunoregulation is likely to be a necessary, but probably not sufficient, feature of SLE. We recognize that this proposition must be considered speculative at this point, but we will accept it for the sake of our current discussions on SLE therapy development.

The basic issues that impede progress in novel SLE therapies may be categorized as the complexity and lack of understanding of the disease; the particular difficulties of drug development for this condition; and the very history of failure. Of course, these categories are all interrelated and overlapping, but will serve as a useful outline.

SLE is a complex and poorly understood disease

The statement is widely appreciated, but it is worthwhile to examine briefly what it entails (6). Perhaps the fundamental lacuna is the failure to explain clearly the etiology and pathogenesis of SLE. Clearly SLE is a largely genetically based, as has been apparent for a number of decades based on identical twin studies (7). More recently, the extraordinary power of genome wide screens (GWS) applied repeatedly to independent databases of patients by large scale (for SLE research, at least) collaborative efforts, have lead to the definitive identification of multiple loci, and probably the genes themselves, that contribute to SLE risk (8,9). In addition, parallel studies in several of the spontaneous mouse models of SLE have also honed in on small genetic intervals or sometimes likely candidate genes (4,10). Many of the genetic findings indeed seem reasonable from a mechanistic standpoint: they identify genes with important roles in the immune system, occasionally in conjunction with functional data of the alleles tested that also fit the paradigm of loss of self tolerance (11,12). Nevertheless, these important advances have so far not allowed us to clarify the underlying pathogenetic mechanisms. The revealed genetic risk factors are multiple; they are diversely distributed in different ethnic groups; and even within groups are usually only present in a minority of patients. Most importantly, the odds ratio or relative risks that they provide for the diagnosis are very modest, almost never >2 and often closer to baseline of 1.0 (no increased risk). This implies that the genetics of SLE are indeed complex, in that the risk for each patient is compounded by modest contributions from at least a handful of loci. It is likely that the epistatic effects of gene interaction might synergize to provide higher risks for certain allelic combinations at different loci, but this remains to be demonstrated. In any case, our current genetic understanding of SLE, either in its human form or in the spontaneous mouse models, cannot begin to construct a mechanistic understanding of disease etiology in even a single patient. Furthermore, it is probably that patients differ among themselves in how they combine individual genetic risk facts, such that in an extreme estimate, every case of SLE might be genetically unique (except, of course, for identical twins).

Important exceptions to this genetic complexity, from both human and murine disease, are highly informative. In humans, it has long been appreciated that complete deficiencies in the early classical complement pathway components (C1q, C1r, C1s, C4 and C2) can imply a very high risk of SLE, perhaps even approaching 100% (13,14). In the mouse world, a few spontaneous mutations, such that the defective *fas receptor* or *fas ligand* genes (*lpr* and *gld*,

respectively) or the translocation of the *tlr7* gene to the Y-chromosome (*Yaa*), also can strongly influence the loss of tolerance to nuclear antigens (4). Furthermore, it is striking the number of engineered genetic defects (“knock outs”) or overexpressed transgenes that can by themselves lead to loss of B-cell tolerance in otherwise normal background mouse strains. Although in many of these latter models the extent of the autoimmunity may be modest both in terms of penetrance and disease severity, the combination of two induced genetic defects can often be shown to result in a greatly enhanced syndrome. If so many gene mutations can promote SLE by themselves, why are such unigenic syndromes not observed more in the outbred human populations? We might speculate that genetic SLE with a high penetrance and Mendelian inheritance would be subject to strong evolutionary counterselection, particularly given that the disease occurs so often in the child bearing years.

What else then contributes to disease development, beyond the underlying genetic risks? The textbooks always list environment as an important factor, but in fact only UV light has been generally excepted as a contributing element, although recent data also suggest that a nearly-ubiquitous virus, EBV, might also play a facilitating role (15–20). In three mouse models, NZB, pristane and MLR/*lpr*, gnotobiotic studies have ruled out a major role of microflora, and in the latter strain, even exogenous antigens in general appeared to play only a secondary role (21–23). Otherwise, epidemiological studies in SLE have failed to show clustering or convincing correlations that might depend on meaningful underlying pathogenetic mechanisms. Our own bias is that random or stochastic effects are essential to disease development in each individual with a permissive genetic background. This effect was strikingly modeled in the anti-Sm response in MRL/*lpr* mouse strain, whereby identical genetic backgrounds led to high titers of this SLE specific autoantibody in a reproducible 25% of the population (24). Unfortunately, such stochastic mechanisms are even harder to elucidate and thus unlikely to lead to therapeutic insights, at least in the near future.

Thus, the genetic analyses, in their complexity, have failed to give us clear directions for targeted therapy development. If in the vast majority of human SLE the contribution of individual risk alleles is so modest, it appears unlikely that gene therapy, *i.e.* an effort to correct the aberrant allele or at least its downstream manifestations, would be efficacious even in selected patients that have the risk allele, and certainly not in the larger population. But fortunately the analysis does not end there. The identification of contributory genes, either by finding small risk alleles in GWS or by ‘proof of principle’ demonstration with robust induced genetic modifications in transgenic mice, means that the physiological pathways influenced by such genes are critical to the maintenance of self tolerance to nuclear antigens. For example, the *stat4* locus clearly has alleles that make SLE more likely (25,26). It is unlikely that any given patient has SLE solely because of a *stat4* mutation, although the deletion of this gene in transgenic mice can have a profound effect in blocking disease (27–29). Since the pathogenic effect (as reflected in the odds ratio for the risk allele) is so modest for this gene, it is unlikely that providing the low risk allele would provide much therapeutic benefit in a sick patient. Furthermore, as cited above, most SLE patients do not have the high-risk allele (30). However, the genetic data do indicate that *stat4*-dependent pathways are important in the loss of tolerance characteristic of SLE, and therefore that targeting this pathway might provide therapeutic benefit. For example, some of the small molecule *jak* inhibitors now being developed for the treatment of RA would be expected to influence Stat4 signaling, and thus would downregulate the identified pathway. The problem then becomes, which pathways to target, based on the dozen or so genes that appear to be true SLE risk factors; where in the pathways to intervene; and what kind of agents will be efficacious and relatively non-toxic. The complexity of the problem is large, but certainly very much restricted compared to an approach not informed by the genetic data.

Not only is our understanding of the genetics of SLE rudimentary, but our insight into pathogenesis of most of the clinical manifestations is still limited. The role of anti-DNA antibodies and complement in lupus nephritis was revealed in the 1960's, but although this basic association is undoubtedly correct, it has become increasingly clear that other mechanisms, including other autoantibody specificities as well as cellular infiltration and inflammatory networks, are also important (31). So it may make sense to target specifically anti-DNA antibodies to treat lupus nephritis, but such an approach would likely only effect part of the problem. The LJP394 trials are instructive in this regard. This novel agent contains multiple DNA antigenic epitopes that are attached to a polysaccharide backbone. It is supposed to induce tolerance to DNA, but no clinical evidence supports this contention, and the preclinical mouse data are minimal. Nevertheless, repeated trials with this agent have consistently shown a significant fall in anti-DNA autoantibody titers in treated patients (about 50% decrease), with some suggestions of decreased incidence of renal flares (32–34). Whether this modest change in autoantibody titers is potentially clinically meaningful, and whether the clinical endpoints targeted in trials of LJP394 will ever be convincingly and robustly met, remains to be seen.

Anti-DNA and renal disease is the easy part (!). Beyond this, the effector mechanisms in the pathogenesis of most of the clinical manifestations of lupus are even more mysterious. For example, the skin, joint, GI, vasculitic, lung and myocardial manifestations lack more than speculative insight into their inflammatory pathways. Hematologic cytopenias can be autoantibody related, but this connection is of little use clinically, and may not apply in many cases. Anti-phospholipid antibodies are apparently involved in pathologic thromboses, some gestational abnormalities, and marantic endocarditis, but the details of the mechanisms are just beginning to be described (35). CNS disease remains a major clinical problem, and potential pathogenic mechanisms have been discussed at various times, some recently, but a comfortable understanding of the roles of autoantibodies, complement, immune complexes, etc. still eludes us (36). Thus, although the production of panels of autoantibodies clearly defines lupus in a certain sense, and many of these autoantibodies probably are important as effectors, as well as diagnostic biomarkers, many of the essential disease pathways continue to defy experimental clarification and are undoubtedly more complex and subtle than we presently perceive. The GWS and the transgenics in the murine SLE models can tell us that a particular gene is important in the pathogenesis, but how the identified genes' proteins fit into the pathogenic pathways, and in which cases the mouse findings are applicable to human disease, in general remain to be determined. We can still target therapies based on genetic data, but not knowing why or how a particular targeted agent might be expected to work limits our ability to focus on the most likely candidates.

The process of drug development is difficult in lupus

A number of features of lupus as a disease entity have made the discovery of novel therapies particularly difficult. The issues related to trial design in lupus have been discussed in some depth recently (1,37). The complexity of the disease, as discussed above, not only has limited our insights into its pathogenesis, but also presents us with patient populations that are bewildering in their inhomogeneity. In the absence of any pathognomonic markers, the gold standard for the diagnosis of SLE, *in the context of a clinical trial*, is the American College of Rheumatology revised criteria published in 1982 and updated in 1997 (Table 1) (38,39). Since only 4/11 criteria need to be met to constitute a diagnosis of SLE, 330 diagnostic combinations are theoretically possible, and obviously two patients could each separately satisfy criteria with not one overlapping item. In fact, there are 5775 unique ways such a disparate pair could be constructed. Certainly, such probability calculations are somewhat disingenuous, since despite the rule for applying the 11 criteria equally to meet the four required, some criteria are 'more equal' than others (40). For example, nearly every lupus patient will have a positive ANA at some point, whereas only a minority would satisfy the CNS criterion. Beyond the eleven

official criteria, all of the other potential manifestations of lupus are also highly variable in their presence in particular patients. Furthermore, different ethnic populations appear to have different patterns of disease, both in terms of prevalence and severity (41–43). Whether this extreme diversity implies that lupus is not a disease, but a syndrome, as has been argued, is beyond the scope of this review (44). The point is that this inhomogeneity confounds the design of a clinical trial to show drug efficacy.

Six aspects of inhomogeneity are particularly troublesome to protocol design (Table 2). First, inclusion and exclusion criteria need to be chosen in a way that permits efficient recruitment. If limited, well defined, aspects of disease involvement are selected, such as active renal disease, then the selection of patients to include in the trial should be relatively straightforward, but the accessible population will be limited to a minority of all lupus patients. This limitation can be counterbalanced by combining multiple trial sites utilizing the international rheumatology community. If the trial aims at recruiting potentially all lupus patients, at least with sufficient disease activity (see below), then the inclusion criteria need to rely on one of the multisystem disease activity scoring paradigms, such as the BILAG or SLEDAI (45–48). Each of these methods has its strengths and weaknesses, but inevitably involves various compromises that end up including or excluding patients inappropriately, based just on clinical judgment.

A second constraint implicit in disease inhomogeneity is apparent in the choice of outcome measures. As in recruitment design, focusing on single organ system involvement can circumvent this limitation, as kidney disease outcomes can be defined as response or flare with a limited number of relatively objective measures of renal function and inflammation. However, if we wish to enroll from the wider lupus population, the outcome measures must use instead the multisystem disease activity scores, and their inevitable weakness. For example, the outcomes measures need to equate the marked improvement of extensive skin disease in one lupus patient with the return to normal of the platelet count of another patient. Are these both equivalent degrees of improvement (or flares, if we look for worsening of disease)? The existent activity scores have various ways to do this, either by scoring each organ system separately in terms of improvement vs. exacerbation, as in the BILAG, or by assigning numbers to each disease manifestation and just adding up the numbers for an overall score, as in the SLEDAI. These methods give us a quantitative rubric in which to deal with the disease diversity, but they do not insure that equal numbers (or letters in the case of the BILAG) are truly equivalent from one patient to another. The systems have been validated in the sense that they correspond to clinical decision making or can be shown to permit appropriate distinctions to be made in some trials. But how much ‘noise’ do they add to our analyses and thus weaken our ability to prove efficacy of a novel compound? Of course we cannot say for sure, but it is reasonable to assume that this factor is not trivial.

A third drawback of the unusual variability of disease manifestations in the lupus population is apparent when one considers that this variability obviously must have biological counterparts in the pathogenic pathways in each patient. It is likely that certain targeted therapies will be more appropriate to patients with particularly biological mechanisms than others. Unfortunately, given our limited understanding of the complexity of disease pathogenesis in lupus, we do not yet have much power to categorize such biological variabilities, other than by clinical or laboratory manifestations (but see discussion of biomarkers, below). Thus, even if we can satisfy ourselves that we can reliably and efficiently recruit and judge a diverse set of patients in a clinical trial, it may be that only certain subsets of patients are theoretically susceptible to clinical benefit from a particular therapy. The lumping together of these patients with others who are biologically resistant to the tested drug would clearly dilute the power of the study and could easily prevent primary efficacy endpoints from showing statistical differences. Of course, this argument probably applies to any drug trial in any disease

population, but the evident great extent of obvious pathological diversity in lupus makes it particularly relevant. *Post hoc* clinical subset analyses of trial data can potentially suggest lupus populations that might particularly benefit from (or not benefit from) a given drug, but given the number of such subsets in a given lupus trial, the numbers of subjects in any given subset will often be small, and in any case additional trials with preselected subsets would be required to prove anything. The alternative of starting with a clinical subset is inefficient, since by chance one might very well chose the wrong (*i.e.*, non-responsive) subset out of the many possibilities for initial trials, and it is not feasible to test each organ system sequentially. Renal involvement is perhaps the best exception to this restraint, since this organ system is involved relatively frequently and seriously, and provides especially useful objective outcome measures. However, if pivotal trials are limited to one or two organ systems, then the eventual approval for the new therapy would be similarly constrained.

A fourth feature of lupus disease variability is the unpredictability of disease course in a given patient. This inevitably increases the background noise that reduces the statistical power of a trial. If moderately to severely sick patients are selected for a trial, many of the placebo treated group will improve either as a result of their background therapy or as 'regression to the mean'. A high placebo response rate of course limits the range in which the tested new drug can show an efficacy signal. If relatively well patients are recruited, then many will not be expected to flare (a reasonable outcome measure in such a trial), so again the window in which efficacy can be shown is restricted. Various options to increase the probability of flare in the study population have been proposed, such as selecting only patients who show a rise in anti-DNA titers (49,50). Again, the gains in statistical power must be weighed against the losses in potential recruitment.

A fifth trial limitation imposed by the heterogeneous nature of the lupus populations is an ethical one. In testing a novel agent, one of the key early concerns is naturally safety. Even though preclinical testing and early phase I/II trials would necessarily have failed to reveal serious safety signals, uncommon but devastating adverse events have been detected only in larger (usually phase III or IV), as in the case of Tysabri in multiple sclerosis (51) trials or in post-marketing surveillance, as for the infliximab and other anti-TNF agents (52). Even for a compound that is already approved for other indications, and widely used with good safety experience, *e.g.*, rituximab, the extension of the use to lupus as a novel, unapproved indication, means that additional agent-related serious adverse events might be encountered. Thus, one must consider that the trial subjects are exposed to some unquantifiable risk by taking the new agent. Given the wide spectrum of disease severity in lupus (and its unpredictability over time), how sick should the study population be? If one wants to limit exposure to those patients who individually may have something to gain from the trial (if the agent is active), then one would focus on the more gravely involved population. Unfortunately, these would be the patients most likely to have serious adverse events during the trial (many of them not related to the therapy), and these patients would be predicted to show more variability in the natural course of their disease over the period of the trial. One avoids these concerns if the study focuses on a population with very mild disease, but then these relatively well patients are being exposed to a drug that they may not need at the time, and that may not even benefit them in the long run if they have persistently mild disease. This dilemma may be illustrated by considering the use of autologous bone marrow transplantation (ABMT) for lupus. This modality has reasonably extensive experience in cancer patients, so we have a good idea of the types and degrees of problems associated with it (53). It is clearly an expensive, highly invasive therapy with a nontrivial mortality/morbidity. There is also a growing literature documenting uncontrolled use of this approach for perhaps several hundred patients with rheumatic diseases, including lupus (54–57). There is even preclinical data in murine lupus models, although here we would claim this calls for more caution (our unpublished results) (58). The NIH has now funded a multicenter controlled trial for ABMT, which is ongoing (59). How would one select

patients for a trial for such a aggressive therapy? Ideally, one would want those patients who suffer from life-threatening disease, and who have exhausted other alternatives. How are such individuals identified? Generally, they are already critically ill and likely suffering from serious toxicities from their attempted therapies. This is just the kind of patient who might be 'too sick' to tolerate a therapy as radical as ABMT. Lupus patients who are not that sick cannot be individually designated as having a disastrous prognosis, even though a number of clinical and laboratory factors have been found to be relatively predictive in a population. So how can one justify subjecting such patients to a risk of mortality of ~5%, plus multiple morbidities, with an unproven therapy which they very well may not need? Therefore, few patients would be so ill that their would justify ABTM, and yet be stable enough to tolerate the stem cell mobilization and immune suppression required. A painful quandary that hamstrings our efforts to try to prove the efficacy of what could be a promising therapeutic approach!

Finally, the unpredictable clinical course of lupus by itself provides an additional barrier to a successful drug trial. Lupus patients can have sudden exacerbations of their disease in any one of their organ systems. If the patient becomes critically ill, such an episode would be characterized as a 'Serious Adverse Event' (SAE) in the context of proper clinical trial. The problem is whether the trial investigators and safety monitors can be certain that the SAE is NOT due to the compound being tested. With the SLE syndrome itself being so variable, and the interactions of the tested drug with this patient population still being investigated, it is necessary to err on the side of safety, even to the point of stopping or significantly modifying the trial until the concerns can be adequately addressed. This occurred in our phase I/II open label rituximab trial, in which our first patient developed marked sinus bradycardia, asymptomatic, within a day after her second dose of rituximab, associated with a high titer of human anti-chimeric antibodies (HACA)s (60). Although the etiology of the slow heart rate was never proven, the trial was halted for about one year, and the dosing protocol was changed. During the much larger EXPLORER randomized control trial for rituximab, the report of two cases of progressive multifocal leukoencephalopathy in SLE patients treated with rituximab, off label and not in the context of the trail, also resulted in an important protocol modifications. In these cases it is even less clear whether the drug was at all contributory, for a variety of reasons, but the cautious approach was not to rule it out (61).

What about the animal models?

In one way the lupus research community is fortunate, in that there are many animal models of the disease in mice (62). These models reproduce much of the serology of human SLE, as well as some of the pathological features, such as the renal disease. The diversity of these models even mimics the complexity the human disease. However, the translations of insights in the murine system to humans is not usually straightforward. Some of the mechanistic studies, for example with type I interferons, are contradictory in different models (63–65). As mentioned above, some of the demonstrated genetic elements in the murine models have failed to find important parallels in human disease. Furthermore, the best-studied mouse models show a progressive, unrelenting course that is not characterized by the remitting/exacerbating pattern seen in most human patients (66). A number of therapies have been tried in mouse lupus and shown to be very effective, particularly if they are given before the age of disease onset (67). However, even in studies that are explicitly treatment, rather than prevention, the degree of efficacy seen in the murine disease appears to surpass grossly what can be achieved in humans. The mouse models will continue to be very useful, since the mechanisms of their disease can be probed in ways impossible in the human population. Then such mechanisms can be focused on in human disease, and if confirmed to be relevant, the implicated pathways can suggest targets for new therapies. Such therapies can then be tested in the mouse models, but the results should not be applied too stringently to predict what compounds might work best in humans, and therefore be subject to further development.

Biomarkers to the rescue?

Part of the difficulty in developing lupus drugs is attributable to the paucity of reliable biomarkers (68). Biomarkers are objective measures, usually laboratory tests, that correlate reliably with disease activity, therapeutic effect, or response to therapy. To be truly useful in clinical trials, then should be validated to predict clinical outcomes, particularly outcomes that would be acceptable (to the FDA and other regulatory agencies) as meaningful endpoints on which to base labeling decisions (69,70). Thereby they can become surrogate markers. For example, renal failure, resulting in death, dialysis or transplantation, is a clear clinical event whose prevention would be the goal of therapy in renal lupus. However, the time it would take for a statistically useful number of treated lupus nephritis patients to reach renal failure precludes any large trial from using such an endpoint. Therefore, biomarkers that reflect glomerular filtration rate, such as creatinine clearance or serum creatinine, can be used to describe surrogate outcomes that should be predictive of renal failure. Thereby, failure to achieve renal remission, occurrence of renal flare, or deteriorating renal function, could all be incorporated into drug trials of manageable durations (≤ 2 years) and produce outcomes that could demonstrate that a novel agent is efficacious, and *would be expected to prevent renal failure in patients who are shown to respond over the limited time period of the trial.*

Other biomarkers could usefully indicate that a compound is having its expected biological effects. For example, if a B cell depleting agent is given, it would be useful to know that B cells are indeed depleted, although it then becomes an issue whether the easily-measured compartments of B cell numbers, such as the peripheral blood, are indicative of B cell depletion at the site(s) necessary for therapeutic effect. To cite another example, anti-Type I interferon therapy is being tried, in part because many lupus patients have an 'interferon signature' consisting of increased mRNA or protein levels from genes known to be regulated by Type I interferons (71,72). The expected biological effect of such a therapy would be the suppression of transcriptional effects of interferon. If such changes could be demonstrated in treated patients, we could be reasonably confident that the doses used are sufficient and the agent is hitting the appropriate target. This biological effect can then be compared to the clinical effects on disease activity, providing more reliable insight into whether the drug has efficacy in lupus and whether the inevitable variable outcomes in different patients can be predicted by the pharmacodynamics in each case.

A variation on this mechanism would be the use of biomarkers to predict which patients are in fact responding to a therapy before the clinical response becomes manifest. Again, the interferon signature might provide such a biomarker by showing 'improvement' early in the course of therapy. One could also imagine that other anticipated changes in gene or protein expression downstream of a chosen target might provide sufficient variability in individual patients that they could be predictive of an incipient improvement in disease activity. We don't currently have such biomarkers. We would hope that they would be found by examining appropriate mechanistic data in controlled efficacy trials, based on sophisticated laboratory measurements that are particularly relevant to the drug being tested. Because of the ease of sampling of urine, the potential to define such biomarkers is particularly enticing for renal involvement (73).

Another use for biomarkers would be to help choose *a priori* which patients might benefit from a given therapy. Such biomarkers might be levels of inflammatory proteins, such as cytokines or chemokines (74,75); gene expression, as in the interferon signature; cellular subsets, as in the stages of B cells that predominate in the peripheral blood (76–78); or even germ line polymorphic alleles that might alter drug metabolism, as for azathioprine (79), or drug activity, as FcγR mutations (80,81). Some trials already make use of such predictive biomarkers, as in the case of the LJP394 DNA mimic (82,83). In a sense, such predictive biomarkers would allow

us to categorize disease subsets in the lupus population, so that only those patients who are most likely to respond to a given agent would be entered into the trial. If that then leads to a successful trial, we would want to confirm that our chosen biomarkers are indeed predictive of response to a given drug. If so, then clearly the clinical use of the agent would benefit from prescreening patients. All very logical! But to date we generally don't have such biomarkers for lupus patients, despite much active ongoing research.

Lupus patients are different

To make matters even worse, not only are lupus patients complicated, diverse, and difficult to predict, but as a group they seem to respond differently to new therapies. Our experience with rituximab is illustrative (60,76). Rituximab is a chimeric, genetically engineered monoclonal antibody with heavy and light chain variable regions from a mouse hybridoma directed at the pan-B cell surface antigen CD20 (84). It has been approved for treatment of B cell lymphomas since late 1997, and thus has an extensive world-wide safety experience of over 1,000,000 patients. Beginning soon after its initial licensing, it has been tried in a number of autoimmune disorders, and achieved an additional label indication for rheumatoid arthritis in 2006 (85, 86). We and others have published small series of lupus patients treated as part of phase I/II uncontrolled trials or anecdotally (87). Although these initial experiences have been quite hopeful, and the drug was gaining increasing usage off-label for lupus unresponsive to traditional therapies, the first of two large multicenter randomized controlled efficacy trials, EXPLORER, completely failed to meet its primary or secondary outcome measures (presented at the ACR, 2008). Whether this failure is due to some combination of the many difficulties with lupus trials as discussed in this review, or whether the drug truly is not efficacious for lupus patients, is still unknown. The completed study was for non-renal lupus with a BILAG-based primary outcome. Data should be available from a second trial, LUNAR, in renal lupus, in 2009. If it shows efficacy, we need to rethink the mechanistic implications for renal lupus versus other organ system involvement. If it again fails to prove efficacy, or worse, to even suggest a useful trend, then we need to rethink our understanding of what B-cell depletion means, as monitored in the peripheral blood, or what role B cells play in the pathogenesis of lupus (3).

Beyond the issue of efficacy, obviously of overriding importance, are the unusual interactions of the lupus patients with the administered rituximab. First of all, the pharmacokinetics and pharmacodynamics were much more variable than what had been seen in patient populations with other diagnoses (60). Generally, it is pretty predictable that administering ~1 gm of rituximab over a 2–3 week period will achieve peak plasma levels in the 200–400 µg/ml level, a terminal half life of 19–21 days, and a consequent persistence of the drug in the circulation until at least 6 months, with plasma levels around 1–10 µg/ml at that point (88–90). We found that many lupus patients failed to maintain blood levels of rituximab beyond 3–4 months. Similarly, the general experience with the effects of rituximab on peripheral blood B cells is complete depletion (≤ 5 B cells/ μ L) one month after completion of therapy, and maintenance of such depletion up to 5 months later (6 months after initiation of therapy). In our series, many of the lupus patients either failed to achieve full depletion, or saw the return of peripheral blood B cells well before six months. Finally, the development of HACA, which indicates an immune response by the treated patient to rituximab, most likely an anti-idiotypic response, was rarely seen in other treated patient populations ($\leq 3\%$ of the time) and then almost only in low titers of 100 ng/ml or less (91). In our trial, about 1/3 of the lupus patients developed HACAs to the drug, sometimes in enormous titers up to nearly 30,000 ng/ml, and sometimes associated with adverse events, including serum sickness. Others have published similar experiments regarding lupus and rituximab, and have suggested that the Fc γ RIIIa polymorphism associated with lupus (phe¹⁵⁸ $\rightarrow$ val¹⁵⁸) may play a role (81,92). Our data and others' suggest that these abnormalities in pharmacokinetics, pharmacodynamics and HACA immune response might correlate in

individual patients, but we await the availability of the much larger experience of the EXPLORER and LUNAR trials for further clarification.

The curse of history

The lack of a successful demonstration of a novel targeted therapy for lupus in itself is a discouraging fact. Mycophenolic acid, which has gone from the stage of promising anecdotes and uncontrolled experiences to several controlled trials in lupus renal disease that indicate that it is at least as effective as cyclophosphamide in patients with mild-moderate renal disease, is perhaps the best success story of the application of a new therapy to SLE (93–95). But even here severe reservations apply. The effort to obtain a label indication for MMF in renal SLE failed utterly, as it was organized as a superiority trial of MMF v. cyclophosphamide, an enormously high bar, even though there is general agreement that the ‘gold standard’ cyclophosphamide leaves much to be desired in terms of efficacy and safety (96). In fact, cyclophosphamide is the standard of care for lupus nephritis based on small trials from the NIH and ongoing clinical experience, and thus does not have a label indication for this use (97–99). This paradoxical situation of having only a non-approved standard of care complicates trial design from the FDA’s point of view.

There have indeed been a number of successful controlled trials in SLE, which have supported efficacy of certain combination regimens or known therapies. For example, hydroxychloroquine has been shown to be effective in maintaining disease remission in general or preventing renal flares in particular (100). Most of the other controlled trials have been limited to renal involvement (101,102). So it is not impossible to run a positive therapeutic trial in SLE (103). Unfortunately, all of the efforts to demonstrate efficacy of truly novel agents with known targets have failed, as listed in Table 3. Many of the novel therapies currently in development look very promising in terms of biological efficacy, target rationale, preclinical data, or safety and efficacy data in related diseases. Type I interferon and IL-6 are good examples. It seems highly likely that in this list, or certainly in some of the other directions which have not been advanced as far up to now, there are agents which would have excellent disease-modifying potency for at least some lupus patients. The issue is whether we will be able to demonstrate this efficacy before exhausting the interest and financial commitment of the pharmaceutical industry for the unmet need in a modest-sized potential market. Of course, our patients are waiting too, and they have even more reason to have limited patience!

ABBREVIATIONS

SLE	systemic lupus erythematosus
s RCT	randomized controlled trial
GWS	genome wide screens
ABMT	autologous bone marrow transplantation
SAE	serious adverse event
HACA	human anti-chimeric antibody

References

1. Strand V, Kimberly R, Isaacs JD. Biologic therapies in rheumatology: lessons learned, future directions. *Nat Rev Drug Discov* 2007 Jan;6(1):75–92. [PubMed: 17195034]
2. Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. *Clin Exp Rheumatol* 2008 Sep–Oct;26(5 Suppl 5):S72–9. [PubMed: 19026147]
3. Eisenberg R, Looney RJ. The therapeutic potential of anti-CD20 “what do B-cells do?”. *Clin Immunol* 2005 Dec;117(3):207–13. [PubMed: 16169773]
4. Kono DH, Theofilopoulos AN. Genetics of SLE in mice. *Springer Semin Immunopathol* 2006 Oct;28(2):83–96. [PubMed: 16972052]
5. Nusinow SR, Zuraw BL, Curd JG. The hereditary and acquired deficiencies of complement. *Med Clin North Am* 1985 May;69(3):487–504. [PubMed: 3892188]
6. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008 Feb 28;358(9):929–39. [PubMed: 18305268]
7. Block SR, Winfield JB, Lockshin MD, D’Angelo WA, Christian CL. Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. *Am J Med* 1975;59(4):533–52. [PubMed: 1101680]
8. Rhodes B, Vyse TJ. The genetics of SLE: an update in the light of genome-wide association studies. *Rheumatology (Oxford)* 2008 Nov;47(11):1603–11. [PubMed: 18611920]
9. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXX, KIAA1542 and other loci. *Nat Genet* 2008 Feb;40(2):204–10. [PubMed: 18204446]
10. Mohan C. Murine lupus genetics: lessons learned. *Curr Opin Rheumatol* 2001;13(5):352–60. [PubMed: 11604588]
11. Kariuki SN, Kirou KA, MacDermott EJ, Barillas-Arias L, Crow MK, Niewold TB. Cutting edge: Autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. *J Immunol* 2009 Jan 1;182(1):34–8. [PubMed: 19109131]
12. Abelson AK, Delgado-Vega AM, Kozyrev SV, Sanchez E, Velazquez-Cruz R, Eriksson N, et al. STAT4 Associates with SLE through two independent effects that correlate with gene expression and act additively with IRF5 to increase risk. *Ann Rheum Dis*. 2008 Dec 9;
13. Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. *Autoimmunity* 2007 Dec;40(8):560–6. [PubMed: 18075790]
14. Manderson AP, Botto M, Walport MJ. The role of complement in the development of systemic lupus erythematosus. *Annu Rev Immunol* 2004;22:431–56. [PubMed: 15032584]
15. Maddison PJ. Nature and nurture in systemic lupus erythematosus. *Adv Exp Med Biol* 1999;455:7–13. [PubMed: 10599317]
16. Kuhn A, Bijl M. Pathogenesis of cutaneous lupus erythematosus. *Lupus* 2008;17(5):389–93. [PubMed: 18490414]
17. Bijl M, Kallenberg CG. Ultraviolet light and cutaneous lupus. *Lupus* 2006;15(11):724–7. [PubMed: 17153842]
18. Toussirot E, Roudier J. Epstein-Barr virus in autoimmune diseases. *Best Pract Res Clin Rheumatol* 2008 Oct;22(5):883–96. [PubMed: 19028369]
19. Doria A, Canova M, Tonon M, Zen M, Rampudda E, Bassi N, et al. Infections as triggers and complications of systemic lupus erythematosus. *Autoimmun Rev* 2008 Oct;8(1):24–8. [PubMed: 18703174]
20. Poole BD, Scofield RH, Harley JB, James JA. Epstein-Barr virus and molecular mimicry in systemic lupus erythematosus. *Autoimmunity* 2006 Feb;39(1):63–70. [PubMed: 16455583]
21. Maldonado MA, Kakkanaiah V, MacDonald GC, Chen F, Reap EA, Balish E, et al. The role of environmental antigens in the spontaneous development of autoimmunity in MRL-lpr mice. *J Immunol* 1999;162(11):6322–30. [PubMed: 10352243]
22. Mizutani A, Shaheen VM, Yoshida H, Akaogi J, Kuroda Y, Nacionales DC, et al. Pristane-induced autoimmunity in germ-free mice. *Clin Immunol* 2005 Feb;114(2):110–8. [PubMed: 15639644]

23. Unni KK, Holley KE, McDuffie FC, Titus JL. Comparative study of NZB mice under germfree and conventional conditions. *J Rheumatol* 1975 Mar;2(1):36–44. [PubMed: 1185733]
24. Eisenberg RA, Craven SY, Warren RW, Cohen PL. Stochastic control of anti-Sm autoantibodies in MRL/Mp-lpr/lpr mice. *Journal of Clinical Investigation* 1987;80(3):691–7. [PubMed: 3624484]
25. Sigurdsson S, Nordmark G, Garnier S, Grundberg E, Kwan T, Nilsson O, et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. *Hum Mol Genet* 2008 Sep 15;17(18):2868–76. [PubMed: 18579578]
26. Taylor KE, Remmers EF, Lee AT, Ortmann WA, Plenge RM, Tian C, et al. Specificity of the STAT4 genetic association for severe disease manifestations of systemic lupus erythematosus. *PLoS Genet* 2008 May;4(5):e1000084. [PubMed: 18516230]
27. Xu Z, Duan B, Croker BP, Morel L. STAT4 deficiency reduces autoantibody production and glomerulonephritis in a mouse model of lupus. *Clin Immunol* 2006 Aug;120(2):189–98. [PubMed: 16713741]
28. Jacob CO, Zang S, Li L, Ciobanu V, Quismorio F, Mizutani A, et al. Pivotal role of Stat4 and Stat6 in the pathogenesis of the lupus-like disease in the New Zealand mixed 2328 mice. *J Immunol* 2003 Aug 1;171(3):1564–71. [PubMed: 12874250]
29. Singh RR, Saxena V, Zang S, Li L, Finkelman FD, Witte DP, et al. Differential contribution of IL-4 and STAT6 vs STAT4 to the development of lupus nephritis. *J Immunol* 2003 May 1;170(9):4818–25. [PubMed: 12707364]
30. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med* 2007 Sep 6;357(10):977–86. [PubMed: 17804842]
31. Isenberg DA, Manson JJ, Ehrenstein MR, Rahman A. Fifty years of anti-ds DNA antibodies: are we approaching journey's end? *Rheumatology (Oxford)* 2007 Jul;46(7):1052–6. [PubMed: 17500073]
32. Anolik JH, Aringer M. New treatments for SLE: cell-depleting and anti-cytokine therapies. *Best Pract Res Clin Rheumatol* 2005 Oct;19(5):859–78. [PubMed: 16150407]
33. Zandman-Goddard G, Shoenfeld Y. Novel Approaches to Therapy for SLE. *Clin Rev Allergy Immunol* 2003 Aug;25(1):105–12. [PubMed: 12794265]
34. Carreno L, Lopez-Longo FJ, Gonzalez CM, Monteagudo I. Treatment options for juvenile-onset systemic lupus erythematosus. *Paediatr Drugs* 2002;4(4):241–56. [PubMed: 11960513]
35. Salmon JE, de Groot PG. Pathogenic role of antiphospholipid antibodies. *Lupus* 2008;17(5):405–11. [PubMed: 18490417]
36. Huizinga TW, Diamond B. Lupus and the central nervous system. *Lupus* 2008;17(5):376–9. [PubMed: 18490411]
37. Strand V. Lessons learned from clinical trials in SLE. *Autoimmun Rev* 2007 Mar;6(4):209–14. [PubMed: 17317609]
38. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997 Sep;40(9):1725. [PubMed: 9324032]
39. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982 Nov;25(11):1271–7. [PubMed: 7138600]
40. Petri M. Review of classification criteria for systemic lupus erythematosus. *Rheum Dis Clin North Am* 2005 May;31(2):245–54. vi. [PubMed: 15922144]
41. Uribe AG, McGwin G Jr, Reveille JD, Alarcon GS. What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs. nurture) cohort? Where are we heading? *Autoimmun Rev* 2004 Jun;3(4):321–9. [PubMed: 15246029]
42. Uribe AG, Alarcon GS. Ethnic disparities in patients with systemic lupus erythematosus. *Curr Rheumatol Rep* 2003 Oct;5(5):364–9. [PubMed: 12967518]
43. Lau CS, Yin G, Mok MY. Ethnic and geographical differences in systemic lupus erythematosus: an overview. *Lupus* 2006;15(11):715–9. [PubMed: 17153840]
44. Albert DA, Munson R, Hadler NM. Is lupus a syndrome or a disease? *J Clin Rheumatol* 2000 Dec;6(6):318–20. [PubMed: 19078492]

45. Yee CS, Farewell V, Isenberg DA, Rahman A, Teh LS, Griffiths B, et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2007 Dec;56(12):4113–9. [PubMed: 18050213]
46. Yee CS, Isenberg DA, Prabu A, Sokoll K, Teh LS, Rahman A, et al. BILAG-2004 index captures systemic lupus erythematosus disease activity better than SLEDAI-2000. *Ann Rheum Dis* 2008 Jun; 67(6):873–6. [PubMed: 17519277]
47. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005 Jul;44 (7):902–6. [PubMed: 15814577]
48. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992 Jun;35(6):630–40. [PubMed: 1599520]
49. Strand V. A novel means to demonstrate early efficacy of a product in systemic lupus erythematosus. *Curr Rheumatol Rep* 2007 Dec;9(6):427–30. [PubMed: 18177593]
50. Swaak AJ, Groenwold J, Bronsveld W. Predictive value of complement profiles and anti-dsDNA in systemic lupus erythematosus. *Ann Rheum Dis* 1986 May;45(5):359–66. [PubMed: 3487292]
51. Sheridan C. Third Tysabri adverse case hits drug class. *Nat Rev Drug Discov* 2005 May;4(5):357–8. [PubMed: 15902765]
52. Lin J, Ziring D, Desai S, Kim S, Wong M, Korin Y, et al. TNFalpha blockade in human diseases: an overview of efficacy and safety. *Clin Immunol* 2008 Jan;126(1):13–30. [PubMed: 17916445]
53. Zinzani PL. Autologous hematopoietic stem cell transplantation in Non-Hodgkin's lymphomas. *Acta Haematol* 2005;114(4):255–9. [PubMed: 16269866]
54. Marmont AM, van Lint MT, Gualandi F, Bacigalupo A. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. *Lupus* 1997;6(6):545–8. [PubMed: 9256315]
55. Tyndall A, Gratwohl A. Hemopoietic blood and marrow transplants in the treatment of severe autoimmune disease. *Curr Opin Hematol* 1997 Nov;4(6):390–4. [PubMed: 9358994]
56. van Laar JM, Tyndall A. Adult stem cells in the treatment of autoimmune diseases. *Rheumatology (Oxford)* 2006 Oct;45(10):1187–93. [PubMed: 16777856]
57. Alderuccio F, Siatskas C, Chan J, Field J, Murphy K, Nasa Z, et al. Haematopoietic stem cell gene therapy to treat autoimmune disease. *Curr Stem Cell Res Ther* 2006 Sep;1(3):279–87. [PubMed: 18220873]
58. Ikehara S. A novel method of bone marrow transplantation (BMT) for intractable autoimmune diseases. *J Autoimmun* 2008 May;30(3):108–15. [PubMed: 18249091]
59. Burt RK, Traynor AE, Craig R, Marmont AM. The promise of hematopoietic stem cell transplantation for autoimmune diseases. *Bone Marrow Transplant* 2003 Apr;31(7):521–4. [PubMed: 12692615]
60. Albert D, Dunham J, Khan S, Stansberry J, Kolasinski S, Tsai D, et al. Variability in the biological response to anti-CD20 B cell depletion in systemic lupus erythematosus. *Ann Rheum Dis* 2008 Dec; 67(12):1724–31. [PubMed: 18250115]
61. Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. *Arthritis Rheum* 2007 Jul; 56(7):2116–28. [PubMed: 17599729]
62. Fairhurst AM, Wandstrat AE, Wakeland EK. Systemic lupus erythematosus: multiple immunological phenotypes in a complex genetic disease. *Adv Immunol* 2006;92:1–69. [PubMed: 17145301]
63. Santiago-Raber ML, Baccala R, Haraldsson KM, Choubey D, Stewart TA, Kono DH, et al. Type-I interferon receptor deficiency reduces lupus-like disease in NZB mice. *J Exp Med* 2003 Mar 17;197 (6):777–88. [PubMed: 12642605]
64. Hron JD, Peng SL. Type I IFN protects against murine lupus. *J Immunol* 2004 Aug 1;173(3):2134–42. [PubMed: 15265950]
65. Nacionales DC, Kelly-Scumpia KM, Lee PY, Weinstein JS, Lyons R, Sobel E, et al. Deficiency of the type I interferon receptor protects mice from experimental lupus. *Arthritis Rheum* 2007 Nov;56 (11):3770–83. [PubMed: 17968932]

66. Cohen PL, Eisenberg RA. Lpr and gld: single gene models of systemic autoimmunity and lymphoproliferative disease. *Annual Review of Immunology* 1991;9:243–69.
67. Wiesendanger M, Stanevsky A, Kovsky S, Diamond B. Novel therapeutics for systemic lupus erythematosus. *Curr Opin Rheumatol* 2006 May;18(3):227–35. [PubMed: 16582684]
68. Illei GG, Tackey E, Lapteva L, Lipsky PE. Biomarkers in systemic lupus erythematosus. I. General overview of biomarkers and their applicability. *Arthritis Rheum* 2004 Jun;50(6):1709–20. [PubMed: 15188346]
69. Illei GG, Lipsky PE. Biomarkers in systemic lupus erythematosus. *Curr Rheumatol Rep* 2004 Oct;6(5):382–90. [PubMed: 15355751]
70. Illei GG, Tackey E, Lapteva L, Lipsky PE. Biomarkers in systemic lupus erythematosus: II. Markers of disease activity. *Arthritis Rheum* 2004 Jul;50(7):2048–65. [PubMed: 15248202]
71. Bauer JW, Baechler EC, Petri M, Batliwalla FM, Crawford D, Ortmann WA, et al. Elevated Serum Levels of Interferon-Regulated Chemokines Are Biomarkers for Active Human Systemic Lupus Erythematosus. *PLoS Med* 2006 Dec 19;3(12):e491. [PubMed: 17177599]
72. Baechler EC, Batliwalla FM, Reed AM, Peterson EJ, Gaffney PM, Moser KL, et al. Gene expression profiling in human autoimmunity. *Immunol Rev* 2006 Apr;210:120–37. [PubMed: 16623768]
73. Rovin BH, Birmingham DJ, Nagaraja HN, Yu CY, Hebert LA. Biomarker discovery in human SLE nephritis. *Bull NYU Hosp Jt Dis* 2007;65(3):187–93. [PubMed: 17922668]
74. Suh CH, Kim HA. Cytokines and their receptors as biomarkers of systemic lupus erythematosus. *Expert Rev Mol Diagn* 2008 Mar;8(2):189–98. [PubMed: 18366305]
75. Kulkarni O, Anders HJ. Chemokines in lupus nephritis. *Front Biosci* 2008;13:3312–20. [PubMed: 18508434]
76. Sutter JA, Kwan-Morley J, Dunham J, Du YZ, Kamoun M, Albert D, et al. A longitudinal analysis of SLE patients treated with rituximab (anti-CD20): factors associated with B lymphocyte recovery. *Clin Immunol* 2008 Mar;126(3):282–90. [PubMed: 18226586]
77. Odendahl M, Jacobi A, Hansen A, Feist E, Hiepe F, Burmester GR, et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. *J Immunol* 2000;165(10):5970–9. [PubMed: 11067960]
78. Jacobi AM, Odendahl M, Reiter K, Bruns A, Burmester GR, Radbruch A, et al. Correlation between circulating CD27^{high} plasma cells and disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 2003 May;48(5):1332–42. [PubMed: 12746906]
79. Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. *Eur J Clin Pharmacol* 2008 Aug;64(8):753–67. [PubMed: 18506437]
80. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIa gene. *Blood* 2002 Feb 1;99(3):754–8. [PubMed: 11806974]
81. Anolik JH, Campbell D, Felgar RE, Young F, Sanz I, Rosenblatt J, et al. The relationship of FcγRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis Rheum* 2003 Feb;48(2):455–9. [PubMed: 12571855]
82. Alarcon-Segovia D, Tumlin JA, Furie RA, McKay JD, Cardiel MH, Strand V, et al. LJP 394 for the prevention of renal flare in patients with systemic lupus erythematosus: results from a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2003 Feb;48(2):442–54. [PubMed: 12571854]
83. Cardiel MH, Tumlin JA, Furie RA, Wallace DJ, Joh T, Linnik MD. Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled phase III trial. *Arthritis Rheum* 2008 Aug;58(8):2470–80. [PubMed: 18668592]
84. Eisenberg R, Albert D. B-cell targeted therapies in rheumatoid arthritis and systemic lupus erythematosus. *Nat Clin Pract Rheumatol* 2006 Jan;2(1):20–7. [PubMed: 16932648]
85. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006 Sep;54(9):2793–806. [PubMed: 16947627]
86. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite

- methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006 May;54(5):1390–400. [PubMed: 16649186]
87. Eisenberg R. Targeting B cells in SLE: the experience with rituximab treatment (anti-CD20). *Endocr Metab Immune Disord Drug Targets* 2006 Dec;6(4):345–50. [PubMed: 17214580]
 88. Genberg H, Hansson A, Wernerson A, Wennberg L, Tyden G. Pharmacodynamics of rituximab in kidney allotransplantation. *Am J Transplant* 2006 Oct;6(10):2418–28. [PubMed: 16925569]
 89. Cartron G, Blasco H, Painsaud G, Watier H, Le Guellec C. Pharmacokinetics of rituximab and its clinical use: thought for the best use? *Crit Rev Oncol Hematol* 2007 Apr;62(1):43–52. [PubMed: 17287129]
 90. Rodriguez J, Gutierrez A. Pharmacokinetic properties of rituximab. *Rev Recent Clin Trials* 2008 Jan; 3(1):22–30. [PubMed: 18474012]
 91. Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol* 1999;10(6):655–61. [PubMed: 10442187]
 92. Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 2004 Aug;50(8):2580–9. [PubMed: 15334472]
 93. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005 Nov 24;353(21):2219–28. [PubMed: 16306519]
 94. Contreras G, Tozman E, Nahar N, Metz D. Maintenance therapies for proliferative lupus nephritis: mycophenolate mofetil, azathioprine and intravenous cyclophosphamide. *Lupus* 2005;14 Suppl 1:s33–8. [PubMed: 15803929]
 95. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000 Oct 19;343(16):1156–62. [PubMed: 11036121]
 96. Sinclair A, Appel G, Dooley MA, Ginzler E, Isenberg D, Jayne D, et al. Mycophenolate mofetil as induction and maintenance therapy for lupus nephritis: rationale and protocol for the randomized, controlled Aspreva Lupus Management Study (ALMS). *Lupus* 2007;16(12):972–80. [PubMed: 18042591]
 97. Decker JL, Klippel JH, Plotz PH, Steinberg AD. Cyclophosphamide or azathioprine in lupus glomerulonephritis. A controlled trial: results at 28 months. *Ann Intern Med* 1975 Nov;83(5):606–15. [PubMed: 1106278]
 98. Ortmann RA, Klippel JH. Update on cyclophosphamide for systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000 May;26(2):363–75. vii. [PubMed: 10768217]
 99. Houssiau F. Thirty years of cyclophosphamide: assessing the evidence. *Lupus* 2007;16(3):212–6. [PubMed: 17432109]
 100. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2008 Dec 22;
 101. Boumpas DT, Sidiropoulos P, Bertsias G. Optimum therapeutic approaches for lupus nephritis: what therapy and for whom? *Nat Clin Pract Rheumatol* 2005 Nov;1(1):22–30. [PubMed: 16932624]
 102. Clark WF, Sontrop JM. What have we learned about optimal induction therapy for lupus nephritis (III through V) from randomized, controlled trials? *Clin J Am Soc Nephrol* 2008 May;3(3):895–8. [PubMed: 18287258]
 103. Tseng CE, Buyon JP, Kim M, Belmont HM, Mackay M, Diamond B, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006 Nov;54(11):3623–32. [PubMed: 17075807]
 104. Boumpas DT, Furie R, Manzi S, Illei GG, Wallace DJ, Balow JE, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. *Arthritis Rheum* 2003 Mar;48(3):719–27. [PubMed: 12632425]

105. Kalunian KC, Davis JC Jr, Merrill JT, Totoritis MC, Wofsy D. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002 Dec;46(12):3251–8. [PubMed: 12483729]
106. Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, Chatham W, et al. Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. *Arthritis Res Ther* 2008;10(5):R109. [PubMed: 18786258]
107. Furie R. Abetimus sodium (riquent) for the prevention of nephritic flares in patients with systemic lupus erythematosus. *Rheum Dis Clin North Am* 2006 Feb;32(1):149–56. x. [PubMed: 16504827]
108. Westhovens R, Verschueren P. Translating co-stimulation blockade into clinical practice. *Arthritis Res Ther* 2008;10 Suppl 1:S4. [PubMed: 19007424]
109. Eisenberg R. Targeting B cells in systemic lupus erythematosus: not just deja vu all over again. *Arthritis Res Ther* 2006;8(3):108. [PubMed: 16732895]
110. Sela U, Dayan M, HersHKoviz R, Lider O, Mozes E. A peptide that ameliorates lupus up-regulates the diminished expression of early growth response factors 2 and 3. *J Immunol* 2008 Feb 1;180(3):1584–91. [PubMed: 18209054]

Table 1
Revised 1982 Criteria for the Diagnosis of SLE¹

1	Malar rash
2	Discoid rash
3	Photosensitivity
4	Oral Ulcers
5	Arthritis
6	Serositis
7	Renal disorder
8	Neurologic disorder
9	Hematologic disorder
10	Immunologic disorder ²
11	Antinuclear antibody

¹These criteria are fully defined in the original description (39).

²The 1997 update redefined some of the details of the autoantibody specificities included in this criterion (38).

Table 2
Why the inhomogeneity of SLE makes trial design so difficult

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1	Difficulty in defining recruitment parameters
2	Complex outcome measures
3	Variable disease mechanisms
4	Unpredictable course
5	Ethical recruitment dilemmas
6	Unexpected SAEs.
-

Table 3Unsuccessful randomized controlled trials for novel agents in SLE in the 21st Century

Company	Agent	Specificity	Outcome	Reference ⁴
Biogen	BG9588	Anti-D154	Trial stopped for SAEs ¹	(104)
IDEC	IDEC-131	Anti-D154	Endpoints not met	(105)
Aspreva	mycophenolate	Anti-metabolite	Endpoints not met ²	(96)
HGS	belimumab	Anti-BAFF	Endpoints not met	(106)
La Jolla Pharma	abetimus	Multivalent DNA	Endpoints not met	(107)
Genentech	rituximab	Anti-CD20	Endpoints not met	(87)
BMS	abatacept	CTLA4-Ig	Endpoints not met	(108)
UCB	epratuzumab	Anti-CD22	Trial stopped for manufacturing issues ³	(109)
TEVA	edratide	DNA idiotype	Endpoints not met	(110)

¹Three patients developed serious thrombotic events.

²Failed to show superiority compared to cyclophosphamide.

³No safety concerns were involved.

⁴References cited do not necessarily contain the trial results.