Role of abetimus in systemic lupus erythematosus

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Anti-DNA antibodies and the B cells that produce them play a major pathogenic role in lupus nephritis. Although current immunosuppressive therapy suppresses autoantibody production and B-cell activity, it is often associated with severe side effects. Abetimus, a soluble, synthetic, double-stranded (ds)DNA tetramer, was developed to bind to circulating DNA antibodies and membrane-bound anti-DNA antibodies on B cells, with the goal of removing circulating pathogenic antibodies and inducing B-cell tolerance. Two large clinical trials with this agent have shown promising results in reducing lupus nephritis flares, especially in patients with high affinity anti-dsDNA antibodies. Nevertheless, although safe and well tolerated, the second trial did not reproduce the desired, statistically significant end point. This was probably due to the trial design and, therefore, given its potential efficacy and safety profile, it seems that once dosing is optimized and the responsive patient population is defined, abetimus will be useful in lupus patients at risk of nephritic flares.

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease, usually occurring in young women during their child-bearing years, where the spontaneous production of autoantibodies leads to the formation of immune deposits within tissues to initiate inflammation. Subsequently, engagement of Fc receptors and activation of complement pathways leads to both the infiltration of inflammatory cells and activation of endogenous cells, perpetuating inflammation, stimulating fibrosis and often leading to organ failure. Nephritis is a serious complication leading to increased morbidity [1–3]. Progression to renal failure over the course of several years is relatively common and leads to a shortened life expectancy, despite renal replacement therapy (i.e., dialysis or transplantation). General anti-inflammatory and immunosuppressive therapy has improved overall renal outcomes; however, many individuals still progress to end-stage renal disease (ESRD) and many suffer from severe complications from the anti-inflammatory and immunosuppressive regimens. Ideally, specific therapy targeted at the immune cells responsible for initiating disease activity has the potential to reduce flares and delay organ failure, while limiting drug toxicity.

Keywords: abetimus, anti-DNA antibodies, autoantibodies, lupus, nephritis, renal flare, SLE

future medicine

Rationale

Although many autoantibodies and immune cells contribute to immune deposit formation and inflammation in lupus nephritis, anti-double-stranded (ds)DNA antibodies are important contributors [4]. These are often elevated in the serum during nephritic flares and are enriched in the eluates of nephritic kidneys. These autoantibodies initially form immune deposits within glomeruli by binding to either endogenous renal antigens (e.g., cross reacting with shared epitopes) or to DNA that has localized previously in tissues (e.g., as nucleosomes via charge–charge interactions through positively charged histones and negatively charged glomerular basement membrane components). More recently, it has become apparent that B cells expressing anti-DNA antibodies are crucial for disease activity, probably by activating autoreactive T cells and macrophages that in turn infiltrate the kidney and contribute to inflammation [4]. Therefore, therapy directed at anti-DNA antibodies, either as soluble circulating proteins and/or on the surface of B cells, has the potential to limit disease activity. Abetimus was produced specifically for this purpose.

Mechanism of action

Abetimus is a synthetic, water-soluble molecule with four ds oligodeoxynucleotides, each attached to a triethyleneglycol backbone, where more than 97% of these oligonucleotides are derived from dsDNA [5]. The drug was designed so that it interacts with anti-dsDNA antibodies. Therefore, it was predicted that following administration the drug would have two major effects: it would form immune complexes with circulating anti-dsDNA antibodies and bind to anti-dsDNA antibodies on the surface of B cells. It was postulated that the formation of circulating immune complexes would

10.2217/17460816.1.2.167 ISSN 1746-0816

prevent immune complex formation in the kidney and thus limit inflammation in the short term [6]. Additionally, it was postulated that interaction of the drug alone with anti-dsDNA antibodies on the surface of B cells in the spleen and lymph nodes (and potentially other tissues) would further limit B-cell activation, since neither costimulatory signals nor local cytokine stimulation would be present in the absence of activated, autoreactive T cells. Efficacy in spontaneous murine lupus nephritis provided support for these postulates; in the BXSB lupus nephritis model, administration of abetimus improved survival and renal pathology [10].

Pharmacodynamics

Abetimus is a synthetic, water-soluble B-cell immunomodulator with four ds oligodeoxynucleotides, each attached to a triethyleneglycol carrier. More than 97% of these oligonucleotides are derived from dsDNA; consequently, the drug only interacts with antibodies capable of recognizing dsDNA [10]. It does not appear to affect T-cell-mediated hypersensitivity or natural killer (NK) T-cell activity against foreign antigens. In preliminary studies in lupus patients, administration of the drug lowered anti-dsDNA antibody levels in a manner that appeared to be dose dependent [5,7,10–12]. Subsequent results suggested that reduction in anti-dsDNA antibody levels depend on the antibody level and affinity of the antibodies for the drug (and DNA).

Clinical trials

To date, there have been a total of at least 12 clinical trials in which 600–700 patients have been exposed to at least one dose of abetimus [8,9,11,13,14]. Among them, two large, separate, randomized, controlled trials have evaluated efficacy of the agent in patients with a history of lupus nephritis. The end points in these trials were the time to renal flare and the incidence of renal flares. The duration of the two major outcome trials, conducted by La Jolla Pharmaceuticals (CA, USA) (termed LJP 394-9-05 and LJP 394-90-09), were 76 and 92 weeks, respectively. These trials enrolled the largest number of subjects (~550 patients). Patients in both trials were well matched for age, gender, race and current therapy (Tables 1 & 2).

The 05 trial was a randomized, double-blind, placebo-controlled, multicenter trial carried out on 230 patients for a mean duration of just over 1 year. The use of prednisone and other immunosuppressive agents were comparable in the groups, prior to study. There was an induction phase where patients received 100 mg/week abetimus or placebo for 4 months, followed by a maintenance phase of three cycles: 2 months off the drug and 3 months at 50 mg/week or placebo. The time to renal flare was significantly less in the abetimus-treated patients, and the difference was particularly apparent among patients with high-affinity anti-dsDNA antibodies.

In the 09 trial, patients were treated with abetimus 100 mg/week or placebo, less than or equal to 22 months without a maintenance phase at a lower dose. The estimated median time to renal flare in the treatment group was 129 months, as compared with 89 months in the placebo group; however, the results did not reach statistical significance. Similar trends toward benefit were observed in the latter trial, with major SLE nonrenal flares for abetimus. Furthermore, the number of patients with 50% reduction in urine protein excretion was greater in abetimus-treated patients than in those treated with placebo. Although not a primary end point, a 50% reduction in proteinuria was seen in both trials with abetimus therapy; however, many patients did not have nephrotic range proteinuria at onset of the trials (i.e., as the trial was not designed to assess the efficacy of the therapy in patients with active nephritis). The latter trial (i.e., LJP 394-90-09) was also confounded by the use of mycophenolate mofetil and this may have reduced the overall flare rate [11].

In both trials, a greater reduction in anti-DNA levels was observed in abetimus-treated patients, and lowering of the titer was associated with a reduction in the renal flare rate. Prevention of flares was most evident in patients with a sustained reduction in autoantibody levels. C3 levels increased in abetimus-treated patients to a greater extent than in placebo-treated patients. Furthermore, there was a greater reduction in flare rate among individuals with elevated serum creatinine levels at onset. Data from the LJP 394-90-05 trial also suggest that there was sustained or improved health-related quality of life as compared with placebo treatment [6].

Side effects: safety

The drug was well tolerated in all trials, with no difference in overall or serious side effects compared with placebo.

Table 1. Abetimus: randomized, double-blind, placebo-controlled, multicenter trials. Incidence of renal flare.

	LJP 349-90-05 (high-affinity group) p = 0.008		LJP 349-90-09 (ITT group) p = 0.401	
	Patients	***Renal flares***	***Patients***	***Renal flares***
Placebo	97	21 (22%)	153	24 (16%)
Abetimus	92	7 (8%)	145	17 (12%)

LJP 349-90-05 and LJP 349-90-09 ITT all patients.
LJP 349-90-05 trial: 230 patients for a mean duration of 371 days. There was a reduction in anti-double-stranded (ds)DNA antibody levels with abetimus treatment ($p < 0.0001$). The estimated median time to renal flare in the trial was 158 months for abetimus compared with 51 months for placebo.
LJP 349-90-09 trial: 317 patients for a mean duration of 310 days. There was a reduction in anti-dsDNA antibody levels with abetimus treatment ($p < 0.001$). The estimated median time to renal flare in the trial for abetimus versus placebo did not reach statistical significance. Overall, in patients with high-affinity anti-dsDNA antibodies, there were fewer renal flares and fewer patients requiring high dose corticosteroid/cyclophosphamide in abetimus-treated patients compared with placebo (both trials).
ITT: Intention to treat; LJP: La Jolla Pharmaceuticals.

Future perspective

The rationale for use of abetimus is derived from observations that anti-DNA antibodies play an important role in the pathogenesis of lupus nephritis. The drug is safe and well tolerated, and its use is associated with a reduction in anti-DNA antibody levels in lupus patients. Combined data from the two large pivotal, intention-to-treat, clinical trials revealed that there was an increase in the time to renal flare and SLE flare in general, and this was especially apparent in patients with high-affinity anti-dsDNA antibodies in serum, which comprised the majority of patients in both trials. Furthermore, overall reduction in anti-DNA antibody titer was associated with benefit. Greater efficacy in this group is probably due, in part, to the effect of the agent as a B-cell immunomodulator, limiting both circulating autoantibody levels and pathogenic B-cell activity. Nevertheless, although the first major clinical trial demonstrated efficacy, benefit in the second trial did not reach clinical significance. The lack of clear-cut benefit in the second trial may have been due to a lower overall flare rate in the group (i.e., patient selection), mycophenolate use, dosing or other factors. Nevertheless, abetimus clearly warrants further study in patients at a high risk of renal flare and disease progression. Given its mechanism of action, it is likely that elucidation of optimal timing and dosing will be critical for use as a B-cell immunomodulator, and in maintaining remission in patients with lupus nephritis who are at risk of flare and developing progressive renal failure. This may require periodic assessment of anti-DNA antibody levels and affinity for optimization in individual patients. Nevertheless, given the potential benefit and lack of side effects, it would seem that it is worth the effort and expense to reduce the rate and intensity of nephritic flares in patients likely to develop them.

Conclusion

The mortality rate is three-times greater in patients with SLE and even greater with nephritis. Anti-DNA antibodies and B cells producing anti-DNA antibodies are pathogenically relevant and provide reasonable therapeutic targets; specific modulation has the potential advantage of greater efficacy and less toxicity than currently available immunosuppressive agents.

Table 2. Abetimus: randomized, double-blind, placebo-controlled, multicenter trials. Incidence of major lupus flares.

	LJP 349-90-05 (high-affinity group) p = 0.009		LJP 349-90-09 (ITT – entire group) p = 0.243	
	Patients	***Major SLE flares***	***Patients***	***Major SLE flares***
Placebo	97	41 (42%)	153	47 (31%)
Abetimus	92	22 (24%)	145	35 (24%)

LJP 349-90-05 trial: 230 patients for a mean duration of 371 days. LJP 349-90-09 trial: 317 patients for a mean duration of 310 days.
ITT: Intention to treat; LJP: La Jolla Pharmaceuticals; SLE: Systemic lupus erythematosus.

Abetimus reduces pathogenic anti-dsDNA antibody levels without affecting normal immunological activities. Abetimus was shown to decrease anti-dsDNA antibody levels in two large clinical trials. In the initial trial, abetimus significantly decreased renal flares; however, in the follow-up trial, the decrease was not statistically significant. A lack of clear-cut efficacy in the second trial may have been related to patient selection, inadequate dosing of the agent and/or use of other immunosuppressive drugs.

Abetimus use was also associated with an improved health-related quality of life. It is a promising therapeutic option. However, patient selection and dosing issues require adjustment to determine efficacy.

Executive summary

Rationale

- Morbidity/mortality rate is high in lupus patients with nephritis.
- The clinical course of lupus nephritis is characterized by disease flares, high-dose steroid use and immunosuppressive therapies.
- Current treatments are limited by toxicity, associated with long-term use, when used to treat and prevent flares.
- There is a need for therapy for lupus patients who are at risk of severe nephritis.
- Anti-double-stranded (ds)DNA antibodies participate in the formation of glomerular immune deposits in lupus patients.
- Abetimus was developed to target circulating anti-dsDNA antibodies and the B cells that produce them. The goal was to provide therapy targeted at major participants in patients with lupus nephritis.

Mechanism of action

- Reduces pathogenic anti-dsDNA antibody levels without affecting the adaptive immune response.
- Suppresses anti-DNA antibody production and anti-DNA antibody-producing B cells.

Clinical trials

- Two pivotal trials, LJP 394-90-05 and LJP 394-90-09, were conducted by La Jolla Pharmaceuticals (CA, USA).
- LJP 349-90-05, a Phase II/III randomized, double-blind, placebo-controlled, multicenter trial of repeated doses of abetimus in patients with systemic lupus erythematosus (SLE) and a history of nephritis, led to a statistically significant reduction in flares.
- LJP 349-90-09, a Phase III randomized, double-blind, placebo-controlled, multicenter safety and efficacy trial of abetimus in SLE patients with a history of nephritis. The reduction in flare rate was not statistically significant.
- Overall, patients with high-affinity anti-DNA antibodies had reduced nephritic flares.
- Abetimus reduced proteinuria and anti-DNA antibody levels.
- Abetimus was safe and well tolerated.
- Abetimus shows promise as an agent to reduce renal flare rate in lupus nephritis patients, although the patient population and optimal dosing require further definition.

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