Expert Opinion

Tovaxin for multiple sclerosis

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Introduction: A potential therapeutic possibility for multiple sclerosis (MS) is provided by Tovaxin, a personalized autologous T-cell immunotherapy utilizing myelin-reactive lymphocytes from peripheral blood.

Areas covered: This review covers the production of the vaccine, which follows a series of steps after the acquisition of T-cells. This includes identification of the subsets that are myelin reactive, expansion *ex vivo* and, also extrinsically, inactivation of their replication capacity by cellular irradiation. Once attenuated, the modified cells are reintroduced into the donor. This process appears to induce a vigorous immune response towards specific populations of autoreactive T-cells determined to attack the myelin and its derivatives by trafficking from the vascular space into the CNS in MS. Historical aspects of the T-cell vaccination with Tovaxin, the process to obtain reactive T-cells and their attenuation techniques *ex vivo* are described. The clinical results obtained from clinical trials are also discussed.

Expert opinion: The process of T-cell vaccination is complicated and presents some limitations. Further studies are required to provide scientific support and clinical evidence of the efficacy of Tovaxin in MS.

Keywords: autoimmunity, autologous, demyelination, myelin, myelin basic protein, T-cell lymphocytes, T-cell vaccination

Expert Opin. Biol. Ther. [Early Online]

1. Introduction

T-cell activation constitutes an essential element in the autoimmune mechanism of certain disorders notably multiple sclerosis (MS), some rheumatoid processes and Crohn's Disease.

According to the predominant theory, genetically predetermined T-cell lymphocytes are activated by specific antigens that may resemble at least a segment of the molecular structure of the myelin components (molecular mimicry) [1], with the eventual subsequent appearance of focal inflammation. In the case of MS, there is still dispute as to whether demyelination and axonal damage are consequences of- or independent concomitant phenomena with the inflammatory process [2]. In rheumatological diseases, the process affects soft tissues and joint structures and, in the case of Crohn's Disease, all the layers of the intestinal wall.

In all these pathologies however, the traffic of activated T-cells from the vascular compartment towards the target structures is considered a fundamental step in the eventual production of tissue damage [3]. Recent reports suggest additional mechanisms for Crohn's Disease including the contribution of altered innate immunity through T_H17 and the influence of ATG16L1 autophagia gene-inductor [4].

The possibility of treatment utilizing immunization with attenuated autologous T-cells extrinsically (*ex vivo*) it has been explored in MS and in animals with experimental autoimmune disease (EAE), experimental autoimmune uveitis, experimental diabetes models and co adjuvant arthritis [5]. This therapeutic projection could be considered for diseases where activation and traffic of T-cell lymphocytes appears to be part of the autoimmune process attacking target organs.

The following provides an opinion on vaccination with T-cells (Tovaxin®, Opexa Therapeutics) in MS (**Box 1**).

10.1517/14712598.2011.584866 © 2011 Informa UK, Ltd. ISSN 1471-2598

Box 1. Drug summary.

Drug name	Tovaxin
Phase	Phase II
Indication	Multiple sclerosis
Pharmacology description	T cell inhibitor
Route of administration	Parenteral, subcutaneous
Pivotal trial(s)	A Phase III pivotal trial is in planning stages (per the sponsor Opexa)

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1.1 Background

It is postulated that within the physiopathology of MS the immune system amplifies its response after recognizing target antigens via antigen presenting cells. Activated T_H1 cells react specifically to one or more putative antigens of the myelin-self and to multiple sclerosis antigens related but not representative of the myelin such as myelin basic protein (MBP), oligodendrocyte glycoprotein associated to myelin (MOG), proteolipid protein (PLP), crystallin αβ and phosphodisterases protein S-100 [6]. Other studies imply also the contribution of T_H-17 cells induced by IL-17 as it occurs in EAE as well as in MS [7].

It is generally accepted that in the subsequent autoimmune cascade course in MS other numerous molecular mechanisms are involved. Some are associated with the release of pro-inflammatory cytokines (T_H1); some with the adhesion of activated T-cells to the luminal surface of endothelial cells of venules within the CNS; then by interaction with adhesion molecules the resulting disruption of the blood–brain-barrier facilitates lymphocytic migration by diapedesis into the CNS.

Once within the CNS other simultaneous immunological phenomena develop including activation of B-cells, complement-mediated histolysis, oligodendrocyte apoptosis and demyelination. This complex autoimmune chain is the result of a coordinated mechanism initiated since its very early phases by genetically determined T-cell lymphocytes activated by molecular mimicry interaction with putative myelin antigens [8].

Multiple genes have been reported to contribute to MS molecular mechanisms and to the susceptibility state of individuals and population groups. The CD58 gene has been described as an important element in the instruction or activation of T-cells [9].

2. Hypothesis

Vaccination or immunization against infections is based on the classic principle of inactivating and artificially attenuating the microbial agent extrinsically. When the attenuated agent is inoculated into the subject, the pathogenic behavior is modified by inducing a protective immunological response.

At present early studies [10] are being conducted with a plasmid-DNA-based vaccine (BHT 3009) that encodes a full-length human MBP peptide. This compound appears to incite a protective immune response in MS by regulating downproliferation of T_H1 pro-inflammatory cells. The concept of this vaccine and its potential clinical effect are still under investigation [11].

Vaccination with autoreactive T-cell lymphocytes in MS is conceptualized as these cells being visualized by the immune system as a pathogen or as antigens, but their potential for replication (therefore subsequent activation by the autoimmune cascade) is suppressed *ex vivo*.

The production process of the vaccine implies that through blood samples obtained from the subject, populations of myelin-reactive T-cells are identified and isolated. Reactivity towards MBP (or other elements of the group multiple sclerosis antigens) is determined utilizing cell lines. These lymphocytes are purified, cloned and expanded numerically, and then subjected to radiation to inhibit cell replication. Once the cells are functionally modified and attenuated through these steps they are re-introduced in the subject through a series of subcutaneous injections. Once in the circulation and having been deprived of their proliferation capacity, the cells are eventually destroyed either by the habitual immune response or by their apoptotic natural cycle (approximately an average of 11.5 days half-life) [12]. Significant decrease in the amount of these lymphocytes in the blood stream potentially would carry a consequent reduction of disease activity.

An additional mechanism of the vaccine (Tovaxin) possibly includes a clonotypic regulation of the network directed to determined targets located in the T-cell receptor (TCR). This would produce at least three types of immune responses: i) acquired, selective and specific immunity to the lymphocytes that participate in the physiopathology of MS; ii) specific recognition of clones and cell lines of immunizing T-cell lymphocytes but not of other T-cells with a different TCR; iii) reactivity to antiidiotypic antibodies [13-15].

The hypothetical proposal of immunization with Tovaxin consists of the therapeutic effect in MS of a T-cell vaccine obtained and processed from a strictly autologous cellular material. Tovaxin would induce regulatory immunity conformed by antiidiotypic cytotoxic T-cells and regulatory T_H2 cells. This effect would result in the consumption of T-cells reactive to myelin and an increment in the regulation of T_H2 anti-inflammatory cytokines.

Nevertheless, the immunological mechanism by the means Tovaxin may provide autologous immunotherapy in MS remains elusive.

2.1 History of immunological studies anteceding Tovaxin. Developing a vaccine

Ben-Nun *et al.* reported in 1981 [16] vaccination against EAE using cell lines made of T-cells reactive to MBP. Animals were protected by inoculation of T-cells that recognized the immunodominating regions of autoantigents to myelin.

Preliminary observations in humans utilizing cells obtained from cerebrospinal fluid in four patients attenuated by fixation with formaldehyde, reported a partial, short-lived immunosuppressing effect evidenced by subsequent responses to stimulation of the CD2 pathway and augmentation of a mixed lymphocytic autologous response. The inoculations were well tolerated [17].

In the course of exploratory studies of natural immunologic 'idiotypic–anti-idiotypic' networks, the specific suppression of T-cells attenuated by radiation o chemical treatment was corroborated. This phenomenon suggested probable induction of inhibiting networks [18].

Sensitized T-cells recognize the 83 – 99 region of MBP with an autoreactive response particularly in individuals that carry the HLA DR2 haplotype. The presence of antigen recognizing motifs utilizing clones of T-cells specific for peptides MBP83 – 99 in restricted panels of HLA $DR2^-$ and $DR4^-$ has been studied using peptides where alanine was substituted. While the recognizing motifs of T-cell clones are present with a great diversity, the residue contacts with the TCR within the 83 – 99 region were noted to be preserved with high consistency. Some of the T-cell clones specific to MBP83 – 99 were able to sustain the alanine substitution but were also susceptible to activation by microbial antigens [19].

T-cells reactive to MBP produce T_H1 pro-inflammatory cytokines (IL-2, TNF-α and IFN-γ among others) facilitating inflammation and myelin destruction in the CNS in MS [20,21]. Additional observations in humans as well as in EAE animal models show that by repeated vaccination with inactivated T-cells regulatory immune responses are induced through anti-idiotypic and anti-ergotypic T-cells [22,23].

Although demyelination antibodies appear to play an important role in the pathogenesis of certain lesions in MS, the inter-relation of this effect with the lymphocyte behavior is not completely elucidated. Studies have shown that B-cells obtained from vaccinated individuals when presented as cell lines in supernatant of Epstein–Barr Virus preparations produce anti-idiotypic antibodies. These antibodies have been found in individuals vaccinated with T-cells, suggesting that their regulatory properties contribute to the suppression of T-cells reactive to MBP [24], but the immunomodulatory effects exerted on B-cells by T-cell vaccination are unknown.

2.2 Cell acquisition

Techniques may vary and in fact undergo continuous updating. The following schemes have been commonly used, not just to obtain and identify the reactive cells but also to activate cell proliferation, implement safety measures in the process and to quantify their numbers (see later).

Multiple blood heparinized specimens are now replaced by a single 350 cc draw (see later). By gradient Ficoll mononuclear cells are separated from peripheral blood (PBMC) [25].

The volume of blood initially required is 300 – 350 ml per patient. However in individuals whose cells are technically difficult to cultivate and clone, additional extractions of variable volume may be needed.

PBMC (200,000 per cell well) are exposed to MBP (40 µg/ml) and to two synthetic peptides corresponding to the immunodominant regions (residues 83 – 99 and residues 151 – 170) respectively at a concentration of 20 µg/ml. The number of cell wells has been predetermined as the optimal cellular density of T-cells reactive to MBP.

Seven days later cultures are restimulated with autologous PBMC pulsed with MBP and the two synthetic peptides mentioned above. The pulsed PBMC are irradiated with 4000 rads before proceeding to the next phase of cell preparation. This radiation phase has been omitted in the new Tovaxin process [26].

2.3 Cell proliferation

Seven days following irradiation, each culture is examined to identify specific proliferation towards MBP and to the synthetic peptides. Cultures are stimulated with [$>^3$H]-thymidine or similar compound and cells collected by an automated cell harvester. Lines of T-cells $CD4^+/CD8^-$ specific for MBP and the synthetic peptides are cloned utilizing a limited dilution process and stimulating the cultures with infusions of recombinant IL-2. In a period of 10 – 12 days the deposits that demonstrate a positive growth are interrogated in order to identify specific clones to MBP. These clones are pre-activated with phytohaemagglutinin (PHA) in the presence of the previously irradiated PBMC. This compound is cultured for 5 – 6 days to be followed by washing with sterile saline solution to eliminate any PHA residue and cell fragments.

3. Technical modifications and safety measures

Use of myelin antigens extracted from bovine brain tissue (or from other origins) potentially carries certain risks, among them, prion disease or immune hyper-response.

In order to enhance the vaccine safety, six synthetic peptides of MBP, PLP and MOG have been reproduced corresponding to the immunodependent epitopes of the myelin antigens: MBPp83 – 99; MBPp151 – 170; PLPp30 – 49; PLPp180 – 199; MOGp1 – 17 and MOGp 16 – 39. During the process of preparation of the product extensive bacterial assay batteries are performed to avoid and detect any potential contamination by bacteria or Mycoplasma. In the case of contamination, the entire process is interrupted and the specimen discarded [26].

Following another irradiation with 8000 rads (in the early studies a ^{60}Co source was utilized), the cells are finally suspended in 2 ml of saline solution as vehicle. It is estimated that 1 ml for subcutaneous injection provides an appropriate number of attenuated cells to provide immunity [27].

3.1 Numerical quantification of reactive cells to MBP

The amount of cells-per-deposit was considered adequate and antigen-specific when counts per minute (c.p.m) were higher than 1500 and exceeded the reference c.p.m (in absence of antigen) for at least three times. According to the protocol described above, the frequency of reactive T-cells is calculated by dividing the number of specific deposits by the total of PBMC cultured initially for each antigen [28]. Diverse methods have been utilized for the analysis of frequencies of reactive T-cells. Some use the entire MBP compound as antigen, measuring cell frequencies 2 to 3 months after having finalized the vaccination.

4. Initial clinical studies

4.1 Vaccination protocol

Patients with MS received subcutaneous injections in each arm (1 ml per administration) at intervals of two months on three occasions (three doses) in the Baylor protocol. The number of cells utilized was extrapolated from the amount calculated in animal studies and varied between 30 million to 60 million cells (two to four clones of T-cells) per injection.

Correale *et al.* [29] had treated four patients with progressive MS utilizing irradiated autologous T-cells stimulated with whole bovine myelin. Each patient received between five and seven injections of attenuated T-cells administered at diverse intervals without observing deleterious effects.

The Baylor Protocol was the first extensive therapeutic study, designed as open Phase II, and performed Baylor College of Medicine, Houston, Texas, USA, for 96 weeks from 1996 to 1999. From the original 114 patients that were initiated on the study only 65 (57%) completed the original protocol [30]. This limitation was mostly due to administrative regulatory and institutional technical dispositions encountered at the time. From this cohort the results in 54 patients (relapsing/remitting MS n = 28. secondary progressive n = 26) that had completed all serial neurological assessments including relapse rate, measurement of the Expanded Disability Status Scale (EDSS) and brain MRI changes over a period of 24 months were studied. This trial, although not controlled, showed a depletion of MBP reactive cells that correlated with a 40% reduction of relapse rate in comparison with pre-treatment rate in the same cohort. EDSS measurements did not show significant changes in the relapsing/remitting group and worsened in the patients in the secondary progressive group. MRI study results remained stable without significant changes ($p > 0.4$) [31]. Since potential clinical benefits appeared to derive from these observations additional studies were planned.

5. Advent of Tovaxin: new techniques and clinical studies

In 2001 the T-cell vaccination patent was acquired by a commercial pharmaceutical company (Opexa Therapeutics, Inc., The Woodlands, Texas, USA; Opexa owns worldwide rights with ability to sublicense). The immunization product was branded 'Tovaxin'. An updated version has been developed escalating the dose and utilizing a trivalent formulation of reactive T-cells to two of the synthetic peptides.

The cell preparation is expanded *ex vivo* basically utilizing the cellular stimuli previously described but the new technique uses only one irradiation session with Cesium 137. The irradiation is carried out on the same day the vaccine will be administered the patient.

The total Tovaxin manufacturing process has an average expected turnaround time of 57 days. Cells are acquired by extracting a constant volume of 350 ml of blood in one single draw, collecting the sample in a sterile plastic bag to initiate the vaccine development process. This includes 7 days to report epitope analysis, 14 days for procurement, 35 days for myelin-reactive T-cell generation and 7 days for quality control. This sequence culminates with the vaccine formulation and dispensation in one day [32].

5.1 Clinical trials with tovaxin

In an open Phase I/II study in 10 patients, incremental doses were administered at baseline and at weeks 4, 12 and 20 (the entire duration of the study was 52 weeks).The median dose of Tovaxin determined to be effective in reducing and depleting reactive T-cells in peripheral blood, was 30 million – 45 million attenuated cells per injection. Unexpectedly, higher doses produced erratic results. The investigators reported only a trend towards EDSS improvement ($p = 0.0561$). The relapse rate in the 2 years preceding the experimental therapy was 1.28 and 0.10 after the completion of the protocol (92% reduction). MRI findings remained stable and were not significant [33].

The study denominated TERMS (Tovaxin for Early Relapsing Multiple Sclerosis) was designed as Phase IIb, multicenter, randomized, controlled and double-blinded trial. The new version of the vaccine was also employed. In this trial 150 patients diagnosed with clinical isolated syndrome (first demyelinating event) and relapsing/remitting MS were randomized in a blinded distribution of 2:1, 100 patients received Tovaxin and 50 placebo, for a duration of 52 weeks. Subcutaneous injections (1 ml) were administered at baseline and at 4, 8, 12 and 24 weeks. The projected primary endpoint was the MRI effect of Tovaxin reducing Gadolinium positive (Gd^+) T1 lesions. Secondary endpoints included changes in the lesion volume of T2 lesions. Both MRI measurements were performed at weeks 28 and 52. Annual relapse rate (ARR) equivalent to one or more attacks was also a secondary endpoint. Results have not been published. A preliminary report at an international meeting indicated the primary endpoint had not been met [34].

Nevertheless, in a prospective analysis study [35] using data from the TERMS study trial, 45 Tovaxin-treatment-naïve

patients with active relapsing/remitting MS compared with 25 placebo patients showed an ARR of 0.18, 64% lower than the ARR (0.50) among placebo patients ($p = 0.046$). In the Tovaxin-treated patients, 76% were relapse-free at one year, compared with 60% of patients in the placebo group; and 91% had stable or improved EDSS compared with 84% of placebo patients. In this study MRI data was not reported.

5.2 Safety and tolerance issues

Tovaxin, as well as earlier versions of the T-cell vaccine, is well tolerated. No serious adverse effects have been reported in 302 patients that have participated in diverse studies including 142 treated with Tovaxin. No immune hyper-responses have been reported. Approximately half of inoculated patients develop a small area of erythema in the injection site that disappears after a few hours.

Frequently during the course of the clinical trials has been noted (although not reported) failure to successfully identify the myelin-reactive T-cells therefore inability to culture and expand them in some patients. Anecdotally several unsuccessful blood extractions in these individuals lead to withdrawl from the trials. The drop-out rates are not emphasized in the recent Tovaxin trials although the manufacturer claims at present that over 850 Tovaxin preparations provide a 99% reproducibility and consistency [32].

6. Conclusion

Tovaxin, as a personalized T-cell vaccination therapeutic possibility for MS, appears to induce a vigorous immune response towards specific populations of autoreactiive T-cells determined to interact with myelin and its derivatives by trafficking from the vascular space into the CNS.

T-cell vaccination in MS has been studied for three decades but the acquisition and identification of myelin-reactive lymphocytes, as well as their attenuation techniques *ex vivo,* still constitutes a rather complex process before the personalized therapy is provided to the patient. Actual data from clinical trials remain short of producing evidence of efficacy. Further studies are required to enhance the scientific hypothesis and to establish a realistic presence of Tovaxin within the current armamentarium of therapies directed to early or relapsing MS as the Phase IIb was designed. Its effect in progressive MS forms also needs to be addressed with controlled studies.

7. Expert opinion

Vaccination in MS with the autologous extrinsically attenuated T-cells product Tovaxin, presents a reasonable and safe if not compelling option in the therapy of MS. Theoretically (as proprosed by the findings of TERMS) the vaccine would be effective in early disease (clinical isolated syndrome) and in relapsing types of MS including therapy-naïve patients. The concepts of utilizing the patient's own cells to produce a vaccine as treatment for MS is substantially attractive even though the production of each individual vaccine requires of a rather involved and prolonged process. With the actual techniques once the blood specimen is obtained it make take as long as 2 months to produce the first dose of Tovaxin.

The current immunological data suggest that the vaccination exerts a modifying effect on some of the basic mechanisms of MS physiopathology where myelin-reactive T-cell lymphocytes play a role, but it is not clear as yet, how this effect interacts with other fundamental components of the pathological process, namely B-cells and antibodies and other known participating elements such dendritic cells, microglia and macrophages.

Some MS patients may not show particularly increased reactivities against known myelin antigens and this could represent a limitation in the design and efficacy of the T-cell vaccination in this population.

Other unanswered questions in view of the lack of published data, involve how long the induced depletion of reactive T-cells will remain in the vaccinated individual (are 'boosters' eventually required?), and, along with these concerns, the necessity to investigate further immunological processes provoked by Tovaxin., More controlled clinical studies extending for at least 96 weeks are indicated. The reported results from the Phase I/II and IIb in ARR and EDSS changes are conflicting. The discrete effect of Tovaxin on MRI activity needs to be revisited and properly addressed, in view that this is an essential parameter of efficacy in clinical trials.

The scientific rationale for vaccination with Tovaxin remains largely theoretical, including confirmation of MBP and other myelin antigens as immunologic target. Only with further studies will the evidence of clinical efficacy of Tovaxin in MS possibly be enhanced and established.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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