REVIEW ARTICLE

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Therapeutic Approaches to Multiple Sclerosis

An Update on Failed, Interrupted, or Inconclusive Trials of Immunomodulatory Treatment Strategies

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Abstract

Multiple sclerosis (MS) continues to be a therapeutic challenge, and much effort is being made to develop new and more effective immune therapies. Particularly in the past decade, neuroimmunologic research has delivered new and highly effective therapeutic options, as seen in the growing number of immunotherapeutic

efficacy or have had to be halted prematurely because of unexpected adverse events. Some others have shown results that are of unknown significance with regard to a reliable assessment of true efficacy versus safety. For example, studies of the highly innovative monoclonal antibodies that selectively target immunologic effector molecules have not only revealed the impressive efficacy of such treatments, they have also raised serious concerns about the safety profiles of these antibodies. These results add a new dimension to the estimation of risk-benefit ratios regarding acute or long-term adverse effects.

Therapeutic approaches that have previously failed in MS have indicated that there are discrepancies between theoretical expectations and practical outcomes of different compounds. Learning from these defeats helps to optimize future study designs and to reduce the risks to patients. This review summarizes trials on MS treatments since 2001 that failed or were interrupted, attempts to analyze the underlying reasons for failure, and discusses the implications for our current view of MS pathogenesis, clinical practice, and design of future studies. In order to maintain clarity, this review focuses on anti-inflammatory therapies and does not include studies on already approved and effective disease-modifying therapies, albeit used in distinct administration routes or under different paradigms. Neuroprotective and alternative treatment strategies are presented elsewhere.

1. Immunopathology of Multiple Sclerosis and Therapeutic Targets

The therapeutic options for multiple sclerosis (MS) have been widened significantly over the past decade. However, the approved therapeutic agents (beta-interferons [IFNβ], glatiramer acetate, mitoxantrone, natalizumab) still have limited efficacy in preventing disease progression, and some of them are associated with either a considerable long-term toxicity or a still unclear risk-benefit ratio. There is a tremendous activity in the search for new therapeutics,[1,2] which is reflected by the soaring number of publications. However, one has to realistically concede that few successful agents in MS stand apart from a large number of therapeutic disappointments.[3-5] Despite rational pathophysiologic concepts, conclusive data from animal models, promising phase I/II studies, and successful application in other autoimmune diseases, several trials testing new compounds in MS patients have shown no benefit. On the other hand, some effective treatments are associated with unexpected or unexpectedly severe adverse effects. Whereas positive studies usually make it into prestigious journals, many negative trials are published merely as abstracts or are not published at all.[6] This is unfortunate because there is a lot to learn from negative results, and a critical reflection is highly important for understanding human MS immunopathogenesis and to help improve future clinical trial design.

We here discuss the pathophysiologic rationale, the experimental basis, and the trial data of novel agents in MS therapy that were not effective and/or were associated with considerable unexpected adverse effects when tested in human phase I–III studies in MS between 2001 and 2010.[1] This review focuses on immunomodulatory strategies; neuroprotective and alternative treatment targets will be discussed in a separate article.

2. Modulation of T-Cell Differentiation and T Helper (T_h)-1/T_h2 Balance

One of the pivotal steps in the initial autoimmune inflammatory pathogenesis of MS is the activation of autoreactive T cells in the periphery via T-cell receptor (TCR)-mediated recognition of major histocompatibility complex (MHC)-I presented antigens – possibly misled by antigenic mimicry. After transmigration across the blood-brain barrier and reactivation in the CNS, both CD4+ T helper (T_h) cells and CD8+ cytotoxic T cells trigger demyelination and primary axonal damage via a shift to a proinflammatory T_h1 cytokine environment.[7] This process seems to be perpetuated by dysregulation of apoptotic mechanisms in T cells. Therefore, modulation of T-cell differentiation and rebalancing of T_h1 and T_h2 response represents a critical mechanism for therapeutic intervention. Broad depletion of autoreactive T cells may be achieved by means of monoclonal antibodies against specific T-cell markers. After the overall negative results with the monoclonal antibodies against CD3 (muromonab CD3) and CD4 (priliximab) in MS trials,[5] other T-cell targets such as CD52

1 Search strategy and selection criteria: studies were identified by a search of PubMed for publications published over the period January 2001 to March 2010, using the terms 'multiple sclerosis' and 'therapy' or 'treatment', and 'trial'. Eligible studies were also identified from conference

and proinflammatory T_h1 cytokines attracted considerable attention (table I).

2.1 Interleukin-12/23: p40 Neutralizing Monoclonal Antibody (Ustekinumab)

2.1.1 Background

Two main proinflammatory populations of CD4+ T cells are T_h1 and T_h17 cells. Interleukin (IL)-12 and IL-23 are two cytokines involved in the differentiation of these two T-cell subsets. IL-12 and IL-23 are closely related, are secreted by myeloid cells and bind to specific receptors expressed on T cells. IL-12 has long been recognized as essential for generation of T_h1 cells secreting interferon-γ (IFNγ), whereas IL-23 has recently been shown to induce a specific T-cell subset producing IL-17.[13,14] Both cytokines are heterodimers consisting of a common subunit (p40) and either p35 (IL-12) or p19 (IL-23). The common IL-12/IL-23 subunit p40 is detected in MS plaques, and administration of IL-12 can induce relapses in experimental autoimmune encephalitis (EAE), an animal model of MS.[15] Therefore, p40 blockade has been expected to be a strategy for modulating autoimmune processes in EAE and MS.[16] Ustekinumab (CNTO-1275) is a human monoclonal antibody directed against the common IL-12/IL-23 p40 subunit that has been shown to prevent clinical disease and development of hyperintense lesions on a T2-weighted MRI in a marmoset model of EAE.[17]

2.1.2 Studies

Tolerability of ustekinumab administered subcutaneously was proven in a phase I trial in relapsing-remitting MS (RRMS) patients.[8] Based on this study, Segal and coworkers[9] tested four widely spread doses (27–180 mg) of ustekinumab in 249 patients with definite RRMS (Expanded Disability Status Scale [EDSS] range 0–6.5) over 19 weeks. Analysis of this randomized, double-blind, placebo-controlled, dose-ranging, phase II study for new gadolinium-enhancing T1-weighted lesions (primary endpoint) revealed no significant difference compared with placebo, for any of the dosage regimens. Regarding clinical parameters, the authors observed no median change in EDSS from baseline to week 23, and most patients developed one relapse but not more than two relapses by week 23 without a significant difference across all subgroups. A high number of adverse events, predominantly infections, were reported in both arms (placebo 78% and verum 83%). However, serious adverse events occurred only in 3% and 2% of the patients treated with

2.1.3 Comment

One possible reason for the negative results found in this study might be a reduced CNS penetration of ustekinumab with subcutaneous administration, since the positive results in the marmoset model of EAE were obtained with intravenous administration. However, active MS lesions are associated with disruption of the blood-brain barrier, which should permit significant penetration of the antibody to potential sites of action. Alternatively, the neutralizing antibody might have been administered outside the therapeutic window, since IL-12 and IL-23 expression in CNS may precede opening of the blood-brain barrier. By contrast, ustekinumab seems to be active in EAE as well as in psoriasis and inflammatory bowel disease, suggesting pathogenic and immunologic differences in these entities. In general, basic differences in the immunopathogenesis of EAE and MS have to be kept in mind, especially concerning the relative importance of T_h17 cells in EAE versus MS.[18]

It may also be possible that distinct actions of the IL-12 heterodimer and its subunits at the IL-12 receptor (IL-12R) result in a lack of effect of this neutralizing antibody. As mentioned above, IL-12 consists of a p40 subunit (which is shared by IL-23) and a p35 subunit forming the IL-12 p70 heterodimer. Levels of IL-12 p40 and IL-12 p70 are independent, and p40 is produced in excess over IL-12 p70 by 5- to 500-fold, which can result in the formation of IL-12 p80 homodimers.[19] The IL-12R consists of a β1 and a β2 subunit, of which only the latter transmits intracellular signals upon ligation.[20] The IL-12 p40 subunit exclusively binds to the IL-12Rβ1 subunit, which lacks signal transmission if the β2 subunit is disengaged. Excess IL-12 p40 is thus able to competitively antagonize binding of IL-12 p70 heterodimer to its receptor.[21] In turn, IL-12 p80 homodimers are able to occupy IL-12R to a higher affinity and block signal transmission by noncompetitive antagonism to IL-12 p70 heterodimers[22] and thus act in an anti-inflammatory way. The functional relevance of antagonization of IL-12 p70 signaling by excess IL-12 p40 monomers or homodimers has been shown *in vitro*.[23,24] Thus, neutralization of IL-12 p40 by ustekinumab might predominantly block the IL-12 antagonizing activity of a p40 excess and outscale the net blocking effect on proinflammatory IL-12 p70 signaling.

2.2 Phosphodiesterase Inhibitors (Ibudilast, Rolipram)

2.2.1 Background

Phosphodiesterases (PDEs) are involved in the regulation of

le I. Modulation of T-cell differentiation and T helper (T_h)-1/T_h2 balance

nt	(Assumed) mechanism of action	Characteristics	Disease course	Outcome		Further/ongoing trials	Comment	Ref./clinical trial ID [NCT…]
				MRI	clinical adverse effects			
2/-23 p40 tralizing ekinumab, O-1275)	Blockade of differentiation of naive T cells to T_h1 cells (IL-12), modulation of macrophage function by blockade of IL-23	Phase I, db, pc, sequential dose escalation; 20 pts	RRMS	High variability in T2 lesion volume and total number of GdEL	Ustekinumab was well tolerated	Finished	Negative results: no clinical efficacy	8
		Phase II, r, db, pc, mc; 249 pts; repeated SC administration	RRMS	Negative, new GdEL	No significant differences for new GdEL T1 lesions and no significant effect on clinical parameters	Finished		9 00207727
inhibitors dilast)	Downregulation of inflammatory responses by changing levels of cAMP and cGMP; shifting the cytokine milieu towards T_h2-driven responses	ol, co; 18 pts	RRMS, SPMS		Negative	Terminated due to lack of clinical efficacy; dose-dependent adverse effects, e.g. nausea and emesis	Regarded as immunomodulating treatment; first-generation of PDE inhibitors with considerable adverse effects; second-generation compounds are improved in this regard	10
vastatin ne or add- IFNβ-1a	Modulation of HMG-CoA reductase-dependent T-cell signaling pathways, shift of T_h1 to T_h2 response	Phase II, ol, btt; 36 pts	RRMS	Reduction in number and volume of GdEL when all or IFN-treated pts were analyzed. No significant effect in pts without IFN	In all pts and all strata, a significantly improved MSFC was found, whereas EDSS was not significantly influenced	Finished	No parallel groups, effect possibly due to IFN treatment, short observation period with low number of pts	11 00616187
		r, db, pc, 0 mg/ 40 mg/80 mg, add-on to IFN; 26 pts	RRMS	Negative; more new T2 lesions or GdEL in verum group (8/17) vs placebo (1/9)	Negative; more relapses in verum group (4/17) vs placebo (1/9)	Finished	High number of pts not adhering to study drug protocol, low number of pts	12

baseline-to-treatment; **cAMP** = cyclic adenosine monophosphate; **cGMP** = cyclic guanosine monophosphate; **co** = crossover; **db** = double-blind; **EDSS** = Expanded Disability Status e; **GdEL** = gadolinium-enhancing lesions; **ID** = identifier; **IFN** = interferon; **IL** = interleukin; **mAb** = monoclonal antibodies; **mc** = multicenter; **mo** = month(s); **MRI** = magnetic resonance ging; **MSFC** = multiple sclerosis functional scale; **ol** = open-label; **pc** = placebo-controlled; **PDE** = phosphodiesterase; **pt(s)** = patient(s); **r** = randomized; **Ref.** = reference; **RRMS** = osing-remitting multiple sclerosis; **SC** = subcutaneous; **SPMS** = secondary-progressive multiple sclerosis.

monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by hydrolysis of the respective cyclic nucleotides. The 11 known PDE subtypes differ in their substrate specificity and their pharmacologic properties, e.g. PDE-4 is activated by elevated levels of cAMP and inhibited by rolipram. Inhibition of PDE reduces tumor necrosis factor-α (TNFα) production by activated monocytes and macrophages, resulting in a lower immune response and a shift of the cytokine milieu to T_h2-driven responses. Treatment with PDE inhibitors has previously shown clinical and histopathologic amelioration in several EAE models.[25] In human MS, the unspecific PDE inhibitor ibudilast was shown to influence cytokine production of T-cell lineages and natural killer cells.[10]

2.2.2 Studies

An open-label, crossover, phase I/II clinical trial of the specific PDE-4 inhibitor rolipram had to be terminated prematurely because of lack of clinical efficacy, after enrolling only eight MS patients. Unexpectedly, the number of contrast-enhancing lesions increased significantly (0.44–1.71 lesions/patient/month), while rolipram was otherwise immunologically active and inhibited T_h1 and T_h17 cells in MS patients.[26] Furthermore, the acceptance of the oral formulation was hampered by dose-dependent adverse effects, e.g. nausea and emesis.

2.2.3 Comment

The first clinical evaluations of PDE inhibitors showed that they have to be regarded as immunomodulating treatment, but they also display considerable adverse effects. However, the observed dissociation between expected immunologic effects and the negative clinical outcome measures raises concerns about the clinical perspective of these drugs. Besides the observed lack of efficacy in MS, clinical development has also been halted in depression, the other major target of PDE inhibitors.[27] The second-generation compounds, which target only a subset of PDE-4 enzymes, are improved in this regard and could perhaps be worthwhile to try in a well designed MS treatment trial.

2.3 HMG-CoA-Dependent T-Cell Signaling: Statins (Atorvastatin)

2.3.1 Background

HMG-CoA reductase inhibitors (statins) are known to have pleiotropic effects *in vivo*, and considerable experimental evidence points towards an immunomodulatory influence pathways in T cells.[28,29] Simvastatin, for example, has been shown to interfere with IL-17 production of human T lymphocytes,[30] and other statins shift the cytokine response towards a T_h2 pattern.[31,32] Moreover, statins interfere with cell infiltration via the blood-brain barrier by downregulation of cell adhesion molecules like lymphocyte function-associated antigen-1 (LFA-1)[33] and reduction of chemokine production by endothelial cells.[34] Statins have also been shown to be effective in the EAE model,[31,35] and it is known from clinical practice that they generally have good tolerability and an excellent safety record. It therefore seemed reasonable to investigate a potential beneficial effect of statins on MS in clinical trials.

2.3.2 Clinical Trials

An early open-label, single-arm, crossover study compared disease activity by MRI in 30 RRMS patients before and after 6 months of treatment with simvastatin.[36] The number and volume of gadolinium-enhancing lesions declined by ~40%. Four years later, a randomized, double-blind pilot study was launched including 26 subjects with RRMS receiving atorvastatin versus placebo as add-on therapy to IFNβ-1a therapy.[12] Surprisingly, statin-treated patients showed a significantly increased relapse rate and an increased number of new lesions as assessed by MRI. These unexpected results are in contrast to other clinical studies, which underline clinical safety and efficacy of statin treatment in MS.[11,36,37]

2.3.3 Comment

A possible explanation for these conflicting data on statins in neuroinflammation might be related to putative proinflammatory and harmful effects of statins. They have been reported to increase IFNγ, IL-12,[38] and IL-12p70[39] production, and to augment the proteolytic activity of matrix metalloproteinases (MMPs).[40] Moreover, statins were shown to hamper CNS remyelination by blocking oligodendrocyte progenitor cell differentiation[41] and mature oligodendrocyte function. In summary, oral add-on therapies with clinically approved agents in other indications, like statins, still represent an attractive strategy for improving MS therapy, but careful studies will be necessary to rule out a putative harmful interaction between statin and interferon treatment in MS.

3. Modulation of T-Cell Activation

Autoreactive T cells in the systemic immune compartment

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