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Therapeutic Approaches in Multiple Sclerosis

Lessons from Failed and Interrupted Treatment Trials

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Abstract

The therapy for multiple sclerosis (MS) has changed dramatically over the past decade. Recent immunobiological findings and current pathophysiological concepts together with advances in biotechnology, improvements in clinical trial design and development of magnetic resonance imaging have led to a variety of evaluable therapeutic approaches in MS. However, in contrast to the successfully introduced and established immunomodulatory therapies (e.g. interferon-β and glatiramer acetate), there have been a remarkable number of therapeutic failures as well. Despite convincing immunological concepts, impressive data from animal models and promising results from phase I/II studies, the drugs and strategies investigated showed no benefit or even turned out to have unexpectedly severe adverse effects.

Although to date there is no uniformly accepted model for MS, there is agreement on the significance of

inflammatory events mediated by autoreactive T cells in the CNS. These can be modified therapeutically at the individual steps of a hypothetical pathogenetic cascade. Crucial corners like: (i) the prevalence and peripheral activation of CNS-autoreactive T cells in the periphery; (ii) adhesion and penetration of T cells into the CNS; (iii) local activation and proliferation and; (iv) de- and remyelination processes can be targeted through their putative mediators. Like a 'specificity pyramid', therapeutic approaches therefore cover from general immunosuppression up to specific targeting of T-cell receptor peptide major histocompatibility (MHC) complex.

We discuss in detail clinical MS trials that failed or were discontinued for other reasons. These trials include cytokine modulators [tumour necrosis factor (TNF)-α antagonists, interleukin-10, interleukin-4, transforming growth factor-β2], immunosuppressive agents (roquinimex, gusperimus, sulfasalazine, cladribine), inducers of remyelination [intravenous immunoglobulins (IVIg)], antigen-derived therapies [oral tolerance, altered peptide ligands (APL), MHC-Peptide blockade], T cell and T-cell receptor directed therapies (T cell vaccination, T-cell receptor peptide vaccination), monoclonal antibodies against leucocyte differentiation molecules (anti-CD3, anti-CD4), and inactivation of circulating T cells (extracorporeal photopheresis).

The main conclusions that can be drawn from these 'negative' experiences are as follows. Theoretically promising agents may paradoxically increase disease activity (lenercept, infliximab), be associated with unforeseen adverse effects (e.g. roquinimex) or short-term favourable trends may reverse with prolonged follow-up (e.g. sulfasalzine). One should not be too enthusiastic about successful trials in animal models (TNFα blockers; oral tolerance; remyelinating effect of IVIg) nor be irritated by non-scientific media hype (deoxyspergualine; bone marrow transplantation). More selectivity can imply less efficacy (APL, superselective interventions like T-cell receptor vaccination) and antigen-related therapies can stimulate rather than inhibit encephalitogenic cells. Failed strategies are of high importance for a critical revision of assumed immunopathological mechanisms, their neuroimaging correlates, and for future trial design. Since failed trials add to our growing understanding of multiple sclerosis, 'misses' are nearly as important to the scientific process as the 'hits'.

1. Immunopathology of Multiple Sclerosis and Therapeutic Approaches

Multiple sclerosis (MS) therapy has changed dramatically over the past decade. Based on the growing immunopathogenetic understanding of MS and with the assistance of modern biotechnology, a growing arsenal of potential therapeutic drugs has been developed. Several agents have been approved and are now being widely used, and a whole battery of new immunomodulatory treatments is currently under development. The methodology of MS trials has evolved in parallel with the therapeutic agents, utilising magnetic resonance imaging (MRI) techniques to great advantage. The sense of excitement in the field of MS therapeutics is reflected by the soaring number of publications (figure 1).

Although to date there is no uniformly accepted model for MS, there is agreement on the significance of inflammatory events mediated by autoreactive T cells in the CNS.[2] These can be modified therapeutically at the individual steps of a hypothetical pathogenetic cascade (figure 2). Crucial steps such as the prevalence and peripheral activation of CNS-autoreactive T cells in the periphery, adhesion and penetration of T cells into the CNS, local activation and proliferation, and de- and remyelination processes can be targeted through their putative mediators (table I). Like a 'specificity pyramid', therapeutic approaches therefore cover the field from general immunosuppression to specific targeting of T-cell receptor peptide major histocompatibility complex (MHC).[3,4] In addition, significant progress has been made in MS clinical trial methodology, which is largely based on advances in nuclear MRI techniques as a 'surrogate marker' in the assessment of potential therapeutic drug effects.[5,6] However, despite rational therapeutic concepts, convincing preliminary animal experiments or positive experiences with other autoimmune diseases, some initial studies showed no proof of efficacy or failed because of unforeseen adverse effects (table II). Whereas the positive trials usually make it into prestigious journals, many negative trials are published merely as abstracts or not at all.[1] This is unfortunate, because there is a lot to learn from a negative result, and critical reflection is highly important for understanding human MS immunopathogenesis and appropriate trial

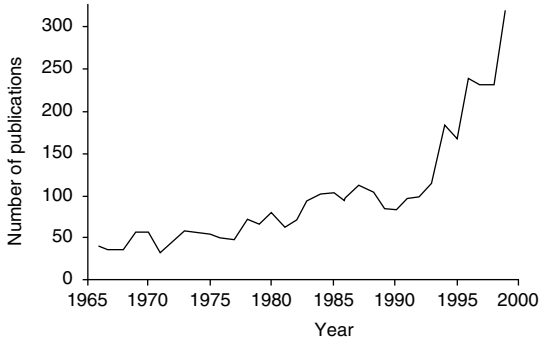

Fig. 1. Number of yearly publications on multiple sclerosis therapy (data from Medline) [reproduced from Hohlfeld et al.,[1] with permission from copyright holders, John Wiley & Sons, Inc.].

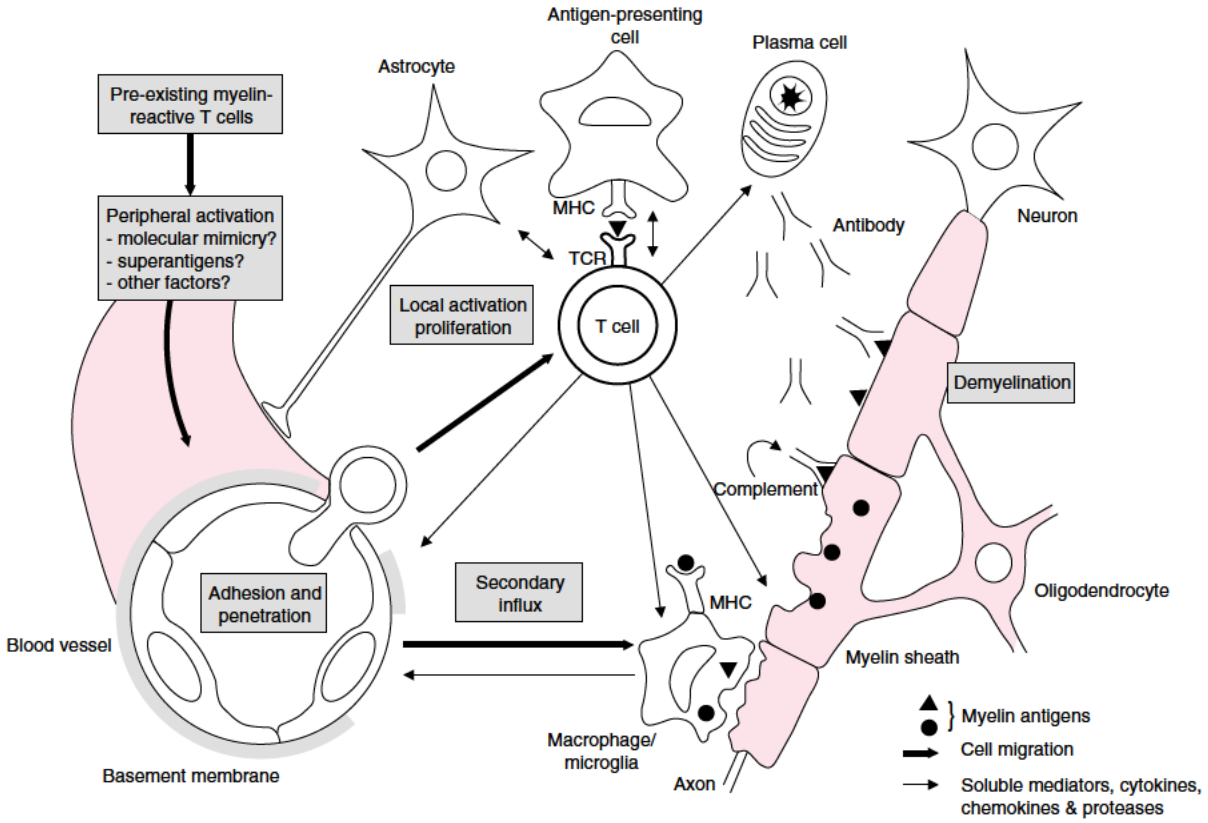

Fig. 2. Crucial steps in multiple sclerosis pathogenesis. Pre-existing autoreactive T cells are activated outside the CNS. The activated T cells traverse the blood-brain barrier and are locally re-activated when they recognise 'their' antigen on the surface of local antigen-presenting cells. The activated T cells secrete cytokines that stimulate microglia cells and astrocytes, recruit additional inflammatory cells, and induce antibody production by plasma cells. Antimyelin antibodies and activated macrophages/microglia cells are thought to cooperate in demyelination. Different steps of the putative immunopathological cascade and different mediators can be targeted therapeutically (see table II) [reproduced from Hohlfeld,[3] with permission from copyright holders, Oxford University Press]. **MHC** = major histocompatibility complex; **TCR** = T-cell receptor.

design. In this review we discuss the immunobiological background, the experimental basis and the clinical studies of some agents and therapeutic strategies in MS treatment which were not effective or led to early trial termination for other reasons.

2. Modification of the Cytokine Pattern

2.1 Tumour Necrosis Factor-α Antagonists

Tumour necrosis factor (TNF)-α, initially characterised for its tumoricidal activity, plays an important role in acute and chronic inflammation (reviewed by Aggarwal and Natarjan,[30] Beutler[31]). TNFα, mainly produced by T cells and macrophages, activates the vascular endothelium and increases permeability. Together with interferon (IFN)-γ, TNFα stimulates the production of nitric oxide (NO) and reactive oxygen derivates, the release of interleukin (IL)-1 and many other cytokines, as well as all metabolites of arachidonic acid. TNFα is one of at least ten (known) members of a ligand family that activates a corresponding family of structurally related receptors.[32] The receptors trigger signals for cell proliferation and apoptosis which play an important role in development as well as in the induction of an immune response.

There are two types of TNF receptors: TNFRI-p55 and TNFRII-p75. They are found either in a transmembrane or in a secreted form, consisting of two subunits, which are stimulated not only by TNFα but also by lymphotoxin-α. Most known biological effects are mediated by the TNFRI-p55 subunit, which binds ligands with a higher affinity than TNFRII-p75. It is important to mention that the receptors are able to mediate different signalling pathways, which partly explains the pleiotropism and the dependence of TNF effects on the cellular context.

Numerous investigations have identified TNFα as an essential pathogenetic factor in different models of experimental aller-

Table I. Examples of recent multiples sclerosis (MS) trials that did not show a convincing clinical benefit (adapted from Hohlfeld and Wiendl,[1] with permission from copyright holders, John Wiley & Sons, Inc.)

Agent	Mechanism of action	MS type (no. of patients) [trial duration]	References	Outcome/MRI	Clinical effect	Problems
Immunosuppressants						
Roquinimex	Synthetic immunomodulator: inhibition of IFNγ and TNFα	RR, SP (715) [terminated early]	7,8	Positive	Positive	Cardiopulmonary toxicity
Sulfasalazine	Anti-inflammatory and immunomodulatory properties	PP, RR, SP (199) [36mo]	9	No sustained effect	No sustained effect	Initially positive effect, absence of long-term benefit
Gusperimus	Interaction with intracellular heat-shock protein (hsp 70) and activation of NF-κB	RR, SP (236) [12mo]	10,11	No effect	No effect	Overall effects unconvincing
Cladribine	Adenosindeaminase-resistant purine nucleoside: induction of long-lasting lymphopenia	PP, SP (159) [12mo]	12-14	Positive[a]	No effect	Discrepancy between MRI and clinical effect; probably no effect on tissue injury
Cytokine modulators						
Lenercept	Soluble TNF-receptor p55: inhibition of TNFα-functions	RR (168) [11mo]	15	No effect	Worsening	Paradoxical effect of TNFα; discrepancy between MRI and clinical effects
Infliximab	TNFα neutralising antibody; human/murine chimeric IgG1: inhibition of TNFα-functions	SP (2) [2mo]	16	Worsening	No effect on EDSS	Paradoxical effect of TNFα
TGFβ2	Immune suppression, pleiotropic growth factor	SP (11) [6mo]	17	No effect	No effect	Bioavailability in the CNS?; nephrotoxicity
IL-10	Recombinant cytokine: inhibition of macrophage APC-function, up-regulation of Th2-cells	RR, SP [terminated]	Unpublished			Insufficient efficacy; possible induction of exacerbations
IL-4 (BAY 36-1677)	Recombinant cytokine: mutein with 2 AA exchanges and selectivity for T, B cells and monocytes, up-regulation of Th2-cells	[terminated]	Unpublished			Insufficient efficacy
Inducers of remyelination						
IVIg (Gamimune® [b]N)	Diverse immunomodulatory effects; in addition, promotion of remyelination in animal model	SDON (55) [12mo]	18	Not done	No overall effect	Remyelination potential may depend on disease activity, timepoint, dose and duration of treatment
		RR, SP (TND) (67) [6mo]	19	No effect[c]	No effect	
		RR (10) [6wk]	20	Not done	No effect	
Antigen-derived therapies						
AI-100	Oral bovine MBP; induction of systemic tolerance via stimulation of antigen-specific regulatory (Th2-, Th3-) cells	RR (30) [12mo]	21	Not done	Possible	
		RR (515) [24mo]	22,23	Not documented	No effect	
Tiplimotide	Altered peptide ligand; peptide analogue of human MBP 83-99	RR (8) [terminated, maximum 9mo]	24	Worsening	Worsening	Interindividual differences in target epitopes (e.g. 'epitope spreading')?; unexpected effects on different T cell populations; allergic reactions
		RR (142) [terminated, 4mo planned]	25	Positive[d]	No effect	
AG284 (DR2:MBP$^{84-102}$)	Soluble HLA-DR2 with a single noncovalently bound MBP peptide	SP (33) [3mo]	26	No effect	No effect	

Table I. Contd

Agent	Mechanism of action	MS type (no. of patients) [trial duration]	References	Outcome/MRI	Clinical effect	Problems
TCR-directed therapies						
T cell vaccination	Attenuated autologous MBP-reactive T cell clones, induction of anticlonotypic T cell responses	RR (8) [22-38mo]	27	Mixed[e]	Mixed[e]	Small number of patients; complexity and diversity of human autoimmune T cells; role of MBP in MS pathogenesis?
TCR peptide vaccination	TCR Vß5.2 (residues 38-58), induction of anti-TCR-regulatory effects	PP, SP (23, all HLA-DRB1*1501 positive) [12mo]	28	Not done	No effect	Small number of patients; marginal effect on disease progression; heterogeneity and individuality of TCR-repertoire and antigen-specificity
T cell inactivation						
Extracorporeal photopheresis	Direct or indirect induction of apoptosis on circulating T cells	SP (16) [18mo]	29	No effect	No effect	Quantities of peripheral CNS-antigen reactive T cells in chronic MS? Relevance of CNS-specific milieu for perpetuation of immune response in chronic MS

a Favourable effect on presence, number and volume of gadolinium-enhanced T1 brain lesions and T2-lesion load,[12] no effect on the T1(hypointense)-lesion volume,[13] or on whole brain volume changes in patients with progressive MS.[14]

b Use of tradenames is for product identification only and does not imply endorsement

c Only a small number of patients (5 of each group) underwent MRI.

d Secondary analysis of patients completing the study and receiving the lowest dose (5mg).

e Beneficial effects on MRI and/or clinical course in 5 patients, worsening of lesions and/or relapses in 3 patients.

AA = amino acid; **APC** = antigen-presenting cell; **EDSS** = Expanded Disability Scale; **IFN** = Interferon; **IgG** = immunoglobulin G; **IL** = interleukin; **IVIg** = intravenous immunoglobulin; **MBP** = myelin basic protein; **MRI** = magnetic resonance imaging; **NF** = nuclear factor; **PP** = primary progressive MS; **RR** = relapsing-remitting MS; **SDON** = stable demyelinating optic neuritis; **SP** = secondary chronic progressive MS; **TCR** = T-cell receptor; **TGF** = transforming growth factor; **Th** = T helper cell; **TND** = targeted neurological deficit; **TNF** = tumour necrosis factor.

gic encephalomyelitis (EAE) and MS. It has been detected in inflammatory CNS lesions; in active lesions it is involved in pathological tissue damage (inflammation as well as demyelination).[33,34] *In vitro* TNFα is cytotoxic for oligodendrocytes. The elimination of TNF-producing macrophages, as well as antagonisation with TNF antibodies, administration of various therapeutic drugs affecting TNFα production (e.g. thalidomide, pentoxifylline, rolipram), or doses of soluble TNF receptor (lenercept), clearly showed a positive effect on pathogenesis and demyelination in various animal models.[35,36]

A series of studies in MS patients showed a correlation of TNF levels in blood, serum or cerebrospinal fluid (CSF) with the clinical course or disease activity.[37-43]

2.1.1 Infliximab (CA2)

In an open phase I study, two patients with a severe secondary chronic progressive form of MS (SPMS) were treated with a monoclonal antibody against TNFα (infliximab).[16] Inflammatory activity as measured by MRI, CSF lymphocytic pleocytosis and IgG index was clearly increased after receiving the infusions. After 2 to 3 weeks, values dropped back to their initial level; the Expanded Disability Status Scale (EDSS) was not altered.

2.1.2 Lenercept

In a phase II study [168 patients with mainly relapsing-remitting MS (RRMS)], the effect of the soluble TNF-receptor immunoglobulin fusion protein lenercept on the development of new lesions in MRI was examined.[15] In this four-armed study, patients received 10, 50 or 100mg of the drug or placebo every 4 weeks (up to 12 months). Baseline MRI was taken as a reference and followed up every 4 weeks (up to week 24 of the study).

MRI showed no significant difference between lenercept and placebo (primary endpoint: cumulative number of new active lesions). However, the number of clinical exacerbations was significantly higher in the lenercept group (annual relapse rate was 0.98 with placebo *vs* 1.64 with lenercept 50mg; p = 0.007). In the

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