IS THERE A ROLE FOR COMBINATION THERAPY IN MS? – YES

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The concept of using combinations of drugs with additive or synergistic properties is well established in the treatment of cancer, hypertension, HIV, infectious, autoimmune and other diseases. This strategy may be particularly feasible in a disease that has a multifaceted pathogenesis such as multiple sclerosis (MS), where existing therapies are only partially effective.

The complex interactions between the immune and the nervous system in MS involve activation of immune cells, endothelial cells, microglia and astrocytes, expression of various cell-surface molecules that mediate cell differentiation, proliferation, activation and migration, and production of cytokines, chemokines, matrix metalloproteinases (MMP), antibodies, complement components, proteolytic enzymes and reactive oxygen species. These concerted events result in inflammation, demyelination and axonal loss within the central nervous system. Incomplete remyelination, regeneration and even neurogenesis may follow, that are usually not sufficient for complete recovery. The complexity and heterogeneity of MS make it unlikely for a single agent to be effective in all patients during all stages of the disease. A considerable proportion of patients will fail existing therapies or progress despite being adequately treated. The combination of drugs with complementary mechanisms of action that target different points along the cascade of pathogenic events, or act on distinct molecular targets within a single cell type or a cellular pathway may result in better suppression of the disease and improved clinical outcomes. Thus, optimization of MS treatment by combination therapy (CT) is a logical strategy.

Ideal combination treatments should include agents with distinct mechanisms of action that:

1. Show additive or synergistic but not antagonistic effects; for example: Statins, which have several immunomodulatory properties (induction of a Th1-Th2 shift, inhibition of proinflammatory cytokines and perhaps neuroprotection) may synergize with glatiramer acetate (GA) or interferon-beta (IFN-β). On the other hand, statins increase MMP activity which may cleave IFN-β, resulting in loss of activity. Indeed, suboptimal doses of GA and atorvastatin that were ineffective when used alone prevented or reversed experimental autoimmune encephalomyelitis (EAE) and induced Th1-Th2 shift when used in combination (Stuve 2006), while the IFN-β-atorvastatin combination worsened MS (Birnbaum 2008). In line with this concept is a study showing that IFN-β-minocycline (an MMP blocker) combination is effective in EAE and attenuates T-cell induced neuronal death in-vitro (Giuliani 2005). IFN-β induced genes that increase activity of certain cytotoxic drugs may explain their beneficial combination effect in clinical trials.
2. Have lessened toxicity because of reduced dosage or antagonistic effects on specific adverse effects (e.g. corticosteroids or pentoxifylline that antagonize the transient induction of IFN-gamma and TNF-alpha during initiation of treatment with IFN-β and may decrease flu-like symptoms), without increased toxicity;
3. Are easily administered;
4. Are safe and well tolerated. The importance of safety was recently demonstrated in the case of natalizumab in combination with IFN-β, where the combination may have contributed to reduced CNS immune surveillance and development of PML.

The rationale for CT can be extended to agents that may prevent the development of neutralizing antibodies (e.g. corticosteroids, immunosuppressants) to the combined therapeutic agent such as IFN-β.

Candidates for CT may include two or more immunomodulators with proven efficacy, immunomodulators plus immunosuppressants to widen the spectrum of therapeutic targets, or immunomodulators plus neuroprotective agents to address both the inflammatory and degenerative aspects of MS. A large body of evidence supporting the use of various combinations of drugs has been accumulated from many in-vitro and animal studies and, most importantly, from clinical trials in MS that are crucial to collect data on efficacy, safety, risks and benefits.

In-vitro combinations

The rationale for CT in MS was initially established in an in-vitro study where IFN-β and GA inhibited the proliferation and pro-inflammatory cytokine (IL-2 and IFN-gamma) production of human T-cell lines specific for myelin basic protein (MBP) in an additive manner. This effect was mediated by complementary modulation of antigen presentation to T-cells: IFN-β decreased activation and MHC class-II expression on antigen presenting cells and non-specifically reduced their ability to activate T-cells reactive to MBP and other antigens, while GA selectively blocked the activation of MBP-specific T-cells only, by binding to the remaining MHC molecules (Milo & Panitch 1995). Another in-vitro combination of sub-optimal doses of GA and atorvastatin resulted in type-II anti-inflammatory cytokine secretion from monocytes that promoted a Th2 differentiation of MBP-specific T-cells (Stuve 2006). An additive effect on monocyte activation has been demonstrated with the combination of GA and minocycline as well (Rugierri 2008). These studies demonstrate additive effects of various combinations of imunomodulaors on immune responses relevant to MS.

Animal studies

While the combination of GA and IFN-alpha was ineffective in EAE (Brod 2000), oral GA and IFN-tau in suboptimal doses had synergistic effect in suppressing EAE (Soos 2002), as did minocycline combined with either GA or IFN-β (Giuliani 2005).

The excellent study by Stuve et al (2006) showed that GA and atorvastatin, which induce Th2 responses through different mechanisms, did not antagonize each other, and the CT (but not monotherapy) with suboptimal doses prevented or

reversed EAE and induced anti-inflamatory cytokine secretion. Recently, CT with minocycline and atorvastatin was shown to be neuroprotective and to suppress EAE (Luccarini 2008).
Although animal data are important, they can't predict what will happen in human patients, but rather support testing these combinations in clinical trials in MS.

Clinical trials in MS

Numerous clinical trials have been conducted with various combinations of immunomodulators, corticosteroids, immunosuppressants (especially mitoxantrone) and other agents. The majority demonstrated the safety and efficacy of the CT, however, none have reached the level required for use in the clinical setting. Among several ongoing phase-III trials, the NIH-funded CombiRx study, comparing copaxone or avonex with the 2 drugs combined in 1000 relapsing-remitting MS patients, may be the first one to provide class-I evidence for CT in MS (DeAngelis 2008).

Conclusions

There is certainly a role for CT that will undoubtedly be part of future MS therapeutics: Rationale and appropriate candidates for CT exist, there is need and several lines of evidence to support CT, and clinical research is moving towards providing class-I evidence for logical CT in MS.

References

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