Are the New Oral Treatments (For MS) Superior to Current Treatments?

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Fingolimod (Novartis) is the first FDA-approved oral disease modifying therapy for MS, having been approved in 2010. However, other oral therapies have been evaluated in phase 2 and 3 clinical trials. They are: cladribine (Merck Serono), laquinimod (Teva), teriflunomide (Sanofi-Aventis), and dimethylfumarate (BG0012, Biogen-Idec). Phase 3 data has been published for two of these agents (fingolimod and cladribine) and phase 2 data have been published and the results of phase 3 studies have been recently announced for the other 3 agents, but phase 3 data are not yet published. Cladribine has been deferred by the United States FDA pending further studies establishing its safety relative to efficacy, and in June, 2011, Merck-Serono announced that it would not pursue registration of this drug further and would stop marketing of the drug in Russia and Australia, where it had been approved for MS.

Undoubtedly, these new oral agents are more convenient for patients than are injectable treatments, especially ones that need to be injected one to three times weekly (interferon beta) or daily (glatiramer acetate). But are they superior? This is a difficult issue to argue. "Oral" drugs being considered as new disease modifying treatments for MS belong to different classes, have different, and in many cases, poorly understood biological mechanisms of action, and have a less established track-record of safety than first generation MS disease modifying treatments. Some, by virtue of their established effects on lymphoproliferation are more likely immunosuppressive than others; one has been shown to have potentially serious toxicities in studies of other indications--cladribine has been implicated in causing secondary malignancies in patients treated with this agent for lymphoreticular malignancies. Therefore, it is difficult to argue that being an "oral" drug per se renders these drugs as "superior". Furthermore, head-to-head comparative trials are relatively few, and comparison of efficacy in different trials that differ in the pools of patients eligible compared to historical trials, in the entry criteria and possibly in the application of outcome measures makes it difficult to compare results directly.

However, as a group, these drugs will be more convenient for patients, and this will likely enhance acceptability and compliance. It is common for patients to stop first generation disease modifying treatments because of persisting flu-like side effects, exacerbation of spasticity and injection site reactions, all common adverse effects of existing therapies. In general, the new oral drugs have infrequent side effects, often not much more frequent than reported by patients taking placebo. Serious adverse effects have tended to be infrequent. Most are associated with low rates of opportunistic infections (although this is true of first generation MS disease modifying treatments too). Unlike natalizumab, also a current treatment for MS, there have been no instances of progressive multifocal leukoencephalopathy (PML). The efficacy with respect to suppression of attacks and MRI's appears to be generally comparable or superior, and the sample size of the pivotal clinical trials is substantially higher than that of the first generation drugs, allowing for robust p values regarding efficacy. Fingolimod has a statistically significant effect on disability progression, whereas the statistical robustness on this outcome measure was modest or non-significant for first generation MS treatments. For some agents, direct head-to-head comparison with an existing disease modifying therapy has been studied (e.g. fingolimod versus interferon beta-1a in the recently published TRANSFORMS study); in the case of fingolimod, it has proven superior in most measures of efficacy compared to intramuscular interferon beta1a.

New anti-epileptic drugs are supplanting first generation anti-epileptic drugs. This is not because of their greater efficacy, but because of their greater tolerability, fewer adverse effects, especially common adverse effects such as sedation and ataxia, lesser interactions with other medications, renal excretion, and better dose-toxicity range. Although the issues are not identical, many parallels could be drawn with the new oral medications for MS. They are likely to supplant existing treatments for MS because of:

1. greater convenience,
2. better tolerability, especially in terms of non-serious adverse events,
3. mechanisms of action that do not involve suppression of lymphocyte proliferation or abrogation of memory,
4. low rates of adverse effects, serious or otherwise.
5. no instances of PML (thus far)
6. superior efficacy to an existing first generation DMT in one case (fingolimod).

A summary of efficacy is shown below from the various published clinical trials. One should be aware of direct comparison of results from trials with different inclusion criteria, with potentially different pools of patients from which they were drawn. Nonetheless, these data provide an impression of the magnitude of benefit of new oral drugs compared to existing drugs.

	Phase	Comparator	Doses	Duration Blinded	% Attack Free	Relative ARR Reduction	Relative Progression Reduction
Fingolimod	3	Placebo	0.5, 1.25	2 y	70% and 75% (vs. 46%)	54% and 60%	87.5%, 88.5% vs. 81% placebo (p= 0.001, 0.004) 6 months confirmed
		Interferon beta 1a IM	0.5, 1.25	1 y	83% and 80% (vs. 69%)	52% and 38%	
Cladribine	3	Placebo	3.5 and 5.25 mg/kg	2 y	80% vs 60% (both doses); OR 2.5	57% and 55%	
BG12	2	Placebo	120 mg QD, 120 mg TID, 240 mg TID	24 wks		32% (240 mg TID)	
Teriflunomide	2	Placebo	7 mg and 14 mg	36 wks		28% and 32%	
Laquinimod	2	Placebo	0.3 and 0.6 mg	72 wks		33% (0.6 mg)	

	Phase	Comparator	Doses	Duration Blinded	Reduction in T1 gad	Reduction in T2 lesions
Fingolimod	3	Placebo	0.5, 1.25	2 y	80% decrease for both doses at 1 y	80% decrease for new/enlarging T2 at 24 months
		Interferon beta 1a IM	0.5, 1.25	1 y	60% and 80% decrease	42% and 38% decrease
Cladribine	3	Placebo	3.5 and 5.25 mg/kg	2 y	60%and 75% CUAL	
BG12	2	Placebo	120 mg QD, 120 mg TID, 240 mg TID	24 weeks	69% (240 mg tid vs placebo)	
Teriflunomide	2	Placebo	7 mg and 14 mg	36 weeks	60% CUAL	
Laquinimod	2	Placebo	0.3 and 0.6 mg	72 weeks	40% (p=0.005)	

References:

Fingolimod
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