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Vedolizumab, a gut-specific monoclonal antibody, renews hope for an alternative to anti-TNF therapy in inflammatory bowel diseases

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Title: Vedolizumab as induction and maintenance therapy for ulcerative colitis

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Journal: *N Engl J Med* 2013;369:699-710

Title: Vedolizumab as induction and maintenance therapy for Crohn's disease

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Summary

Recently, GEMINI 1 investigators examined the efficacy of vedolizumab for induction and maintenance of remission in active ulcerative colitis (Mayo score of 6-12 and unsuccessful previous treatment with azathioprine, steroids or biologic therapy) in two integrated randomized controlled trials (RCTs) [1]. In the induction phase, 521 patients received open-label IV vedolizumab 300 mg at weeks 0 and 2 while 374 patients were blinded and randomized to receive vedolizumab or placebo at weeks 0 and 2. Any of these patients who had a response (defined as a 30% and at least 3 score drop from baseline Mayo Clinic Score) to vedolizumab at week 6 were re-randomized to receive placebo or vedolizumab every 4 or 8 weeks up to week 52. At week 6, clinical remission rate was significantly higher in the vedolizumab treatment group (47.1%) compared with patients in the placebo group (25.5%; P<0.001). At week 52, 44.8% of patients who continued to receive vedolizumab every 4 weeks and 41.8% of patients who continued to receive vedolizumab every 8 weeks remained in clinical remission as compared to 15.9% of patients who transitioned to the placebo arm (P<0.001). After one year, more than half of the patients receiving vedolizumab had mucosal healing compared to 20% of patients in the placebo cohort. At week 52, adverse events were similar among all groups.

In the same issue of the *New England Journal of Medicine*, Sandborn *et al* [2] (GEMINI 2 study group) examined the efficacy of vedolizumab for induction and maintenance of remission in active Crohn's disease (Crohn's Disease Activity Index (CDAI) of 220-450 and unsuccessful previous treatment with azathioprine, methotrexate, steroids or biologic therapy) in two integrated RCTs. In the induction phase, 747 patients received open-label IV vedolizumab 300 mg at weeks 0 and 2 while 368 patients were blinded and randomized to receive vedolizumab or placebo at weeks 0 and 2. Any of these patients who had a response (a drop of 100 points in CDAI) to vedolizumab at week 6 were re-randomized to receive placebo or vedolizumab every 4 or 8 weeks up to week 52. At week 6, clinical remission rate (CDAI ≤150) was significantly higher in the vedolizumab treatment group (14.5%) compared with patients in the placebo group (6.8%; P=0.02); however, response rates were not statistically different (31.4% vs. 25.7%, P=0.23). At week 52, 36.4% of patients who continued to receive vedolizumab every 4 weeks and 39.0% of patients who continued to receive vedolizumab every 8 weeks remained in clinical remission as compared to 21.6% of patients who transitioned to the placebo arm (P<0.01). Higher rates of serious adverse events (24.4% vs. 15.3%) and infections (44.1% vs. 40.2%) were seen in patients who were treated with vedolizumab.

Opinion

Medical therapy of inflammatory bowel diseases (IBD) has been revolutionized in the past two decades. Along with

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better control of symptoms and mucosal inflammation, the course of disease may have changed by recent evidence of decreasing rates of surgical interventions in IBD patients [3]. However, we still have a long road ahead to achieve an optimal management for both ulcerative colitis (UC) and Crohn's disease (CD) and new therapeutic strategies are desperately needed.

Parallel to our advancements in understanding of the pathophysiology of IBD, new therapeutic targets are identified and become commercially available. One of the targets of interest is a family of cell-surface glycoproteins critical for leukocyte adhesion, migration and activation (i.e. adhesion molecules). Most classes of leukocytes, including lymphocytes, monocytes, eosinophils and basophils express α4 integrin adhesion molecules on their cell surface. In the past, targeting both α4β7 and α4β1 integrin subunits (i.e. blocking α4 chains) using natalizumab, a monoclonal antibody, showed promising results in induction and maintenance of remission in large randomized controlled trials (RCTs); however, association of this drug with progressive multifocal leukoencephalopathy (PML), a serious and potentially fatal infection, has extremely limited its use [4]. PML is caused by reactivation of John Cunningham (JC) virus and is considered to be a consequence of abnormal leukocyte trafficking to the central nervous system due to α4β1 integrin subunit inhibition; therefore, the spotlight has focused on vedolizumab, a humanized monoclonal antibody that selectively blocks α4β7 heterodimer which is only present on gut lymphocytes.

While the results at week 52 were positive for both UC and CD, the magnitude of efficacy and safety of the drug was more pronounced in UC patients. This difference may be due to dissimilar nature of UC and CD. Relative to CD, ulcerative colitis is rather limited to the gut and may respond better to a gut-selective immunosuppression such as vedolizumab.

To date, no case of PML has been reported in association with vedolizumab, however, we should closely watch for future developments to see if the risk is truly negligible. Four cases of neoplasia were seen in GEMINI 2 study (appendix carcinoid, basal cell skin carcinoma, breast cancer and squamous cell carcinoma) that warrant extreme vigilance in the future.

A relatively small group of patients receiving vedolizumab develop antibodies (4%) and so far only three infusion reactions have been reported [5]. The role of antibodies in dosing and side effects of vedolizumab should be explored further.

In conclusion, based on some of the largest RCTs ever conducted on IBD patients, vedolizumab seems to be a promising alternative for management of IBD, especially in UC patients. Head to head trials of currently available biologic therapies are required for optimal therapeutic approach to IBD patients. However, such trials will require extensive resources and meticulous collaborative efforts. Until such trials are conducted, Bayesian network meta-analyses may be our best available alternative to compare various treatment options. As the majority of RCTs in IBD have a placebo arm, this method of analysis can indirectly compare the effects of drugs based on a common comparator (i.e. adjusted placebo rate). Unlike other fields of medicine, use of network meta-analyses is not yet widely adopted in gastroenterology but there was a dramatic increase in the number of abstracts with such methodology in the United European Gastroenterology Week and the American College of Gastroenterology conferences which will certainly make their way into gastroenterology journals.

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