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EXPERT REVIEWS

Why did IL-12/IL-23 antibody therapy fail in multiple sclerosis?

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Evaluation of: Segal BM, Constantinescu CS, Raychaudhuri A *et al.* Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing–remitting multiple sclerosis: a Phase II, double-blind, placebo-controlled, randomized, dose-ranging study. *Lancet Neurol.* 7, 796–804 (2008).

IL-12 and IL-23 are two cytokines that appear to play a key role in the pathogenesis of multiple sclerosis. Blocking these cytokines via a neutralizing antibody caused dramatic improvements in animal models of the disease, and Phase I trials found the antibody to be safe in humans. The paper under review is a Phase II clinical trial of ustekinumab, an anti-IL-12/23p40 antibody for treatment of multiple sclerosis. Investigators found no clinical or radiologic improvement in any treatment group compared with placebo controls. We consider the known mechanisms of action for IL-12/23 in multiple sclerosis and suggest that ustekinumab's lack of efficacy was partially due to the study's inclusion of patients with advanced disease. Studies of the antibody in a more limited subset of patients (those with very early disease) might show a treatment effect.

Keywords: IL-12 • IL-23 • multiple sclerosis

Multiple sclerosis (MS) is a devastating disease of the CNS characterized by demyelination and axonal damage. Although its pathophysiology is complex and many details are still poorly understood, the disease appears to be mediated by T cells specific for CNS antigens – also referred to as autoreactive or encephalitogenic T cells – that migrate into the CNS and attack the myelin sheath with subsequent neuronal damage [1]. While there is disagreement as to why these cells develop, two closely related cytokines, IL-12 and IL-23, help them realize their encephalitogenic potential [2,3]. These heterodimeric cytokines each have one unique subunit (IL-12p35 or IL-23p19) and one shared subunit (IL12/23p40). Neutralizing these cytokines via an antibody directed against the shared IL12/23p40 subunit ameliorates experimental autoimmune encephalomyelitis (EAE) in animal models for MS, in both rodents [4–6] and primates [7,8]. The significant treatment effect observed in animal models was the impetus for the clinical trial currently under review [9].

It is important to consider the mechanisms by which IL-12 and IL-23 contribute to demyelinating pathology in order to understand and critique the recent findings in humans. Both cytokines are produced by antigen-presenting cells (e.g., dendritic cells or macrophages) in response to an immune challenge. Once secreted, IL-12 and IL-23 direct the differentiation of naive T cells. T cells exposed to IL-12 differentiate into proinflammatory, IFN-γ-secreting, Th1 cells. While most Th1 cells do not react to self proteins and are effective in clearing infections, encephalitogenic populations can develop and cause demyelination. MS patients have an abnormally high number of Th1-differentiated, autoreactive cells [1]. Similarly, the recently discovered IL-23 causes a population of IL-17-producing T cells to expand. These are sometimes referred to as Th17 cells and are also believed to contribute to an encephalitogenic response [3,4].

In addition to promoting T-cell differentiation, IL-12 promotes their migration into the CNS by upregulating adhesion molecules, including P-selectin glycoprotein ligand (PSGL-1) and the chemokine receptor CCR5 [10,11]. Mates for these receptor/ligand pairs, including P-selectin and CCL3/MIP1α, are expressed significantly in the CNS during the early stages of EAE,

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and neutralizing either receptor/ligand pair limits leukocyte trafficking into the CNS [12,13]. Blocking T-cell transmigration into the CNS has proved an effective strategy for ameliorating demyelinating disease in animal models [13,14] and is the primary mechanism of action for the MS disease-modifying agent natalizumab [15].

Although IL-12 increases the encephalitogenic potential of T cells [2], it is not essential for demyelinating disease. Mice deficient in IL-12p35 can still develop EAE [16]. Mice deficient in IL-12/23p40, however, are not susceptible and neither are those deficient in IL-23p19 [17,18]. Thus, while both IL-12 and IL-23 drive the production and expansion of T cells with encephalitogenic potential, only IL-23 is necessary for the induction of disease in animal models. Interestingly, IL-23 does not appear to be critical during disease maintenance; once encephalitogenic T cells have developed, lack of IL-23 is not protective [19].

Methods & results

The authors of the current study enrolled 249 patients with a diagnosis of relapsing–remitting MS (RR-MS), with an expanded disability status scale (EDSS) score from 0 to 6.5, and at least two MS relapses in the previous 2 years or one relapse in the previous 6 months. No subjects had received any immunomodulating treatments within 3 months of screening. This Phase II study was performed at 38 sites in North America, Europe and Australia. The trial design was randomized, double-blind and placebo-controlled. Enrolled patients were randomly assigned 1:1:1:1:1 to placebo or ustekinumab 27, 90 or 180 mg every 4 weeks or ustekinumab 90 mg every 8 weeks. All patients received subcutaneous injections of placebo or drug weekly from weeks 0–3 (induction phase) and then every 4 weeks during weeks 7–19 (maintenance phase) except for the ustekinumab 90 mg every 8-weeks group, which received drug every 8 weeks with a placebo substitute at weeks 7 and 15. The primary end point was the cumulative number of new gadolinium-enhancing T1-weighted lesions from baseline to week 23 on serial cranial MRI.

Ustekinumab did not show improvement in the primary end point for any treated group versus placebo. Moreover, there were no differences between groups in the number of clinical or objective relapses. There were no changes in the median EDSS scores. A dose-dependent increase in ustekinumab serum concentration was demonstrated, but it was not assessed in cerebrospinal fluid. Adverse effects were observed with similar frequencies in treated patients compared with placebo.

The investigators concluded that, although ustekinumab is well tolerated, it is not effective in reducing the cumulative number of gadolinium-enhancing T1 lesions in multiple sclerosis.

Discussion & significance

This study failed to show any therapeutic benefit when neutralizing IL-12/23p40 in patients with MS. Yet benefit was consistently observed in animal models. Can we conclude from this that, despite preclinical evidence, IL-12/23 does not play a role in human MS? We feel that the subject population and methods chosen for this study may have obscured any true effect that existed. Ustekinumab is unlikely to become a broad-spectrum agent, effective for treating all types of MS; however, future studies may demonstrate a narrower role in treating a subset of patients with very early disease.

When designing a clinical study, it is important to select a patient population appropriate for the drug being tested. In the current study, recruited subjects had a wide range of MS-related disability; indeed, their EDSS scores were as high as 6.5, which means that those patients required constant bilateral assistance (e.g., crutches, walker or braces) to walk 20 m without resting. Such severe disability typically develops after many years of disease, yet, as discussed above, the contributions of IL-12 and IL-23 to pathology all appear to occur in early disease – when naive T cells are first differentiating and migrating into the CNS. Clinically, patients at this stage of disease have mild symptoms or are asymptomatic. Correspondingly, in the preclinical studies leading up to this trial, animals were treated with neutralizing antibody before or very shortly after the first signs of disease [4–8]. Neutralizing the cytokine after years of disease, after naive T-cells have already differentiated into Th1 and Th17 cells and migrated into the CNS is likely far too late to have a clinical effect.

A second consideration is that, although preclinical studies showed that IL-12 upregulated molecules involved in leukocyte trafficking into the CNS [10,11], there is no guarantee that the same mechanisms are at work in humans or that manipulating IL-12 would effectively modify leukocyte trafficking. Indeed, while IL-12-induced PSGL-1 and CCR5 may recruit T cells to the inflamed CNS in humans [20,21], molecules such as α-4β-1 integrin also play a large role [15]. Moreover, since IL-12 is not the only regulatory agent for PSGL-1 and CCR5, neutralizing this upstream molecule is likely to be less effective in decreasing leukocyte infiltration than targeting the adhesion molecules directly.

Finally, it is unlikely that ustekinumab consistently passed the blood–brain barrier (BBB) in this study. Thus, while peripheral IL-12 and IL-23 may have been neutralized, immune cells already in the CNS may not have been affected. Certainly, most antibodies do not enter the CNS when the BBB is intact and, at the start of this study, only approximately 50% of patients exhibited evidence of BBB disruption in the form of a gadolinium-enhancing lesion [1]. This is problematic since IL-12 and IL-23 localize to MS lesions [22,23] and may be playing additional roles at the site of pathology [24].

Expert commentary & five-year view

In our view, while IL-12 and IL-23 likely contribute to the pathogenesis of MS, their primary effect seems to be early in the disease course, driving the differentiation of encephalitogenic T cells and promoting their entry into the CNS.

The therapeutic window for ustekinumab, by extension, would be during very early disease; it would not be expected to modify advanced MS. Indeed, by the time patients experience symptoms, demyelinating lesions may have been present for months or years.

Thus, while a clinical trial of ustekinumab in patients with a clinically isolated syndrome suggestive of MS might yield positive results, it is not surprising that the current study, which incorporated many patients with chronic disease, did not demonstrate benefit. Owing to the lack of clinical signs and symptoms in early MS, IL-12 and IL-23 may not be feasible targets for ameliorating disease, even though it is likely that they are important for disease pathogenesis.

Financial & competing interests disclosure

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