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Anti-Inflammatory Treatments for Major Depressive Disorder: What's on the Horizon?

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Inflammation is associated with greater depressive symptom severity,[1,2] resistance to commonly used antidepressants,[3] differential response to escitalopram versus nortriptyline or bupropion,[4,5] and higher likelihood of hospitalization[6] in patients with major depressive disorder (MDD). While precise mechanisms remain unclear, a recent report found a very high correlation (coefficient = 0.855) between plasma and cerebrospinal fluid levels of C-reactive protein (CRP), suggesting that peripheral measures of inflammation are good indicators of central nervous system inflammation.[7] Since currently available monoaminergic antidepressants are ineffective for over a third of MDD patients,[8] targeting inflammation may be a promising avenue to develop novel mechanistically driven antidepressants.[9] This report briefly reviews published reports and ongoing studies of anti-inflammatory treatments with potential antidepressant effects. While the role of inflammation and anti-inflammatory treatments have gained recent attention in bipolar depression,[10,11] this report is limited in scope to studies in patients with MDD.

What's Currently Available?

Nonsteroidal anti-inflammatory drugs (NSAIDs). Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor NSAID, is the most widely studied NSAID for its antidepressant effect. In a meta-analysis of 4 randomized controlled trials (N = 160), adjunctive celecoxib was associated with 6.6 times higher rates of remission than placebo.[12] However, use of celecoxib as antidepressant augmentation was discouraged in a previous report due to the relatively small sample size for a meta-analysis, limited geographic region for 3 out of 4 studies, and lack of peer review for 1 of the reported studies.[13] NSAIDs have poor clinical utility as antidepressant monotherapy. In a large study[14] of adults with osteoarthritis (N = 1,497), ibuprofen (800 mg thrice daily) or naproxen (500 mg twice daily) and celecoxib (200 mg daily) were statistically superior to placebo in reducing depression severity. However, this difference amounted to reduction of 1 point on the 9-item Patient Health Questionnaire, suggesting lack of clinical significance.[14] In another large study[15] (N = 2,528) of cognitively normal elderly adults (age ≥ 70 years), there was no difference in reduction of depressive symptoms with either celecoxib (200 mg twice daily) or naproxen (220 mg twice daily) as compared to placebo, even among those participants with significant depressive symptoms prior to treatment initiation.[15]

Nutraceuticals. Several nutritional supplements have shown antidepressant potential, especially in MDD patients with increased levels of inflammatory biomarkers. Shelton et al[16] found that L-methylfolate was significantly more effective than placebo in MDD patients with elevated levels of CRP than those with low CRP. In another report, curcumin (500 mg twice daily) was shown to be more effective than placebo over 8 weeks of treatment in MDD patients with elevated levels of leptin.[17] Omega-3 fatty acids, especially eicosapentaenoic acid (EPA), have potent anti-inflammatory properties. In a meta-analysis, supplementation with EPA-predominant formulations was superior to placebo in MDD patients, whereas docosahexaenoic acid (DHA)-predominant formulations had no significant effect.[18] In a report of 155 patients with MDD who had levels of inflammatory marker available, patients with MDD who had high levels of inflammatory marker had greater reduction with EPA as compared to either placebo or DHA.[19] Interestingly, placebo was superior to DHA in those with high inflammation.[19] Omega-3 fatty acids as monotherapy for adolescent depression (N = 51) was not superior to placebo in a recent report,[20] suggesting the need for future studies with larger sample sizes. Nutraceutical supplementation may be effective in subgroups of MDD patients based on age and other comorbid conditions. For example, supplementation with EPA, curcumin, and L-methylfolate may be considered in obese adult MDD patients as both CRP and leptin levels increase with higher body mass index.

Anticytokine treatments. Arguably, monoclonal antibodies against proinflammatory cytokines are the most intriguing anti-inflammatory treatments for depression. These biologics allow precise targeting of specific immune pathways. As our understanding of the role of individual proinflammatory cytokines in pathogenesis of depression becomes clearer, these anticytokine treatments offer a path to personalized medicine. Levels of tumor necrosis factor α (TNF-α), a proinflammatory cytokine, have been reportedly elevated in MDD patients with treatment-resistant depression (TRD). Hence, Raison et al[21] conducted a randomized placebo-controlled trial of infliximab, an anti–TNF-α monoclonal antibody, in MDD patients with TRD. While infliximab (5 mg/kg) was not superior to placebo overall, the authors noted a significant trend where higher CRP levels predicted better outcomes with infliximab. In TRD patients with CRP levels > 5 mg/L, infliximab had significantly better outcomes than placebo.[21] To test the efficacy of anticytokine treatments in patients with chronic inflammation, Kappelmann et al[22] conducted a large meta-analysis using published reports up to April 2016. They found that anticytokine treatments significantly improved depressive symptom severity in patients with chronic inflammatory conditions even after accounting for improvement in primary physical illness. Since April 2016, there have been 3 additional reports that support these findings. Interleukin 17 (IL-17) is a proinflammatory cytokine that has been implicated in pathophysiology of depression and antidepressant

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response.[23,24] Two different monoclonal antibodies targeting IL-17 have been shown to reduce depressive symptom severity. Brodalumab, an anti–IL-17 receptor antibody, significantly reduced both depressive and anxiety symptoms as compared to placebo in a phase 3 study of patients with moderate-to-severe plaque psoriasis.[25] In the subset of patients in this study who had moderate to severe depressive symptoms prior to treatment initiation, rates of remission with brodalumab were 43%–47% as compared to only 9% with placebo.[25] These findings were remarkably similar to those with ixekizumab, an anti–IL-17-A monoclonal antibody. Using data from 3 phase 3 studies, Griffiths et al[26] reported remission rates of 33.6%–45.2% with ixekizumab as compared to a 17.8% remission rate with placebo. Additionally, sirukumab (N = 176) and siltuximab (N = 65), two anti–IL-6 antibodies, have also been shown to be effective in reducing depressive symptom severity among patients with rheumatoid arthritis and multicentric Castleman disease even after controlling for symptom severity of primary illnesses.[27] While the utility of these anticytokine treatments in patients with MDD is currently limited, clinicians may consider them for their patients with comorbid autoimmune conditions such as psoriasis and rheumatoid arthritis.

Other treatments. Several commonly used medications also affect the immune system and have been evaluated for their potential antidepressant properties. In a recent meta-analysis of 165 patients with moderate to severe depression, augmentation with statins (lovastatin, atorvastatin, simvastatin) was associated with significantly greater reduction in depression severity than placebo augmentation.[28] Minocycline, an anti-inflammatory tetracyclic antibiotic, has also been studied for its antidepressant potential in patients with MDD. In an open-label study of MDD patients with psychotic symptoms, augmentation of antidepressant medications (fluvoxamine, paroxetine, and sertraline) with minocycline was associated with significant reduction in both depressive and psychotic symptom severity.[29] Two recent double-blind randomized controlled trials[30,31] tested the efficacy of minocycline (200 mg/d) versus placebo in patients with MDD. In the larger study[30] (N = 71), while there was no significant difference in depressive symptom severity as measured by the Montgomery-Asberg Depression Rating Scale, minocycline was superior to placebo on Clinical Global Impression (CGI) Improvement scores as well as on measures of quality of life and psychosocial functioning. In the smaller study[31] (N = 41), minocycline augmentation significantly reduced depressive symptom severity as measured by the 17-item Hamilton Depression Rating Scale (HDRS-17) and CGI. Utility of minocycline in bipolar depression may also be restricted to those patients with higher pretreatment inflammatory markers such as interleukin 6.[11] Future studies with larger sample size and longer-term outcomes are needed to establish the clinical utility of minocycline augmentation in depression.

What's on the Horizon?

Systemic inflammation induces indoleamine 2,3-dioxygenase enzyme, which diverts tryptophan metabolism away from serotonin synthesis and toward the synthesis of neurotoxic kynurenine metabolites. In animal models, leucine, an essential amino acid, is effective in ameliorating inflammation-induced depression by preventing the uptake of kynurenine at blood-brain barrier.[32] Two ongoing studies are testing the antidepressant potential of leucine in humans. While one is testing the efficacy of a 2-week course of leucine in preventing depressive symptoms induced by a single lipopolysaccharide injection in healthy human volunteers (NCT03557684), another is testing the efficacy of leucine augmentation in a double-blind randomized crossover study of MDD patients who have inadequately responded to their ongoing antidepressant treatment (NCT03079297). Another novel antidepressant being tested is the infusion of mesenchymal stem cells (MSCs) obtained from human donors. These allogenic MSCs have been shown to exhibit immunomodulatory potential. Ongoing studies are testing its efficacy in MDD patients with treatment-resistant depression (NCT02675556) as well as with comorbid alcohol use disorder (NCT03265808). Antidepressant effects of minocycline in MDD patients with treatment-resistant depression are also being tested (NCT02456948). A recently completed pharmaceutical company–sponsored phase 2 study of sirukumab (NCT02473289) is the largest study of its kind (N = 193), testing the antidepressant effect of a monoclonal antibodies in MDD patients with elevated CRP (≥ 3 mg/L) and failure to respond to at least 1 but no more than 3 antidepressant medication trials. Among patients with CRP ≥ 3 mg/L at screening and baseline visits (N = 142), there was no significant difference either in changes in depression severity (baseline to week 12 reduction in HDRS-17) or in response and remission rates at week 12.[33] Higher baseline CRP predicted better response to sirukumab, especially in the domain of anhedonia as measured by the Snaith-Hamilton Pleasure Scale.[33]

Caution in Using Anti-Inflammatory Treatments

While data in humans are lacking, preclinical studies suggest that combining NSAIDs with currently available antidepressants may result in differential outcomes based on the type of antidepressant. While use of ibuprofen blocked the antidepressant effects of selective serotonin reuptake inhibitors and tricyclic antidepressants in animal models, no similar effect was seen with either bupropion or monoamine oxidase inhibitors.[34] Partly consistent with these findings, MDD patients treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study who were on an NSAID were less likely to remit than those not on an NSAID.[34] The risk of opportunistic infections with use of anticytokine treatments is well recognized. Additionally, use of brodamulab was associated with 4 completed suicides in patients with psoriasis, resulting in a US Food and Drug Administration (FDA) black box warning and prescription restriction under a Risk Evaluation and Mitigation Strategy (REMS) program.[35] As reported by Raison et al,[21] anticytokine treatments are inferior to placebo in TRD patients with low inflammation (CRP < 1 mg/L), suggesting that their use should be restricted to patients with ongoing systemic inflammation. Due to the risk of contaminants in nutritional supplements, clinicians should be vigilant about the source of these supplements and prescribe only pharmaceutical grade supplements when available. Finally, as none of the anti-inflammatory treatments are approved by the FDA, clinicians should restrict their off-label use to patients for whom FDA-approved treatments are either ineffective or impractical. In such cases, clinicians should use a measurement-based care approach[36] to monitor improvement in depressive symptom severity along with any treatment emergent adverse events with these anti-inflammatory treatments and ensure that patients are not continued on ineffective treatments for too long.

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