doi:10.36849/JDD.2020.4722

Is Dupilumab an Immunosuppressant?

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ABSTRACT

Atopic dermatitis (AD) is a chronic, immune-related, inflammatory skin disease that significantly reduces quality of life. In severe AD, systemic immunosuppressants are often utilized, though they do not target specific biologic pathways of AD. A non-immunosuppressive treatment may offer the possibility of high efficacy with better safety. Dupilumab, the only FDA-approved biologic for AD (approved for adults and adolescents 12 and older), is a fully human monoclonal IgG4κ antibody that inhibits IL-4 and IL-13 signal. To date, there is no evidence that dupilumab has immunosuppressive effects. On the contrary, by decreasing *Staphylococcus* colonization and partially normalizing the skin microbiome, likely via direct effects on the innate immune system, dupilumab appears to improve immunologic protection against infections. To date, no study has reported reactivation of latent infections (such as hepatitis B or tuberculosis, invasive fungal infection or unusual opportunistic infections) or progression of malignancy in association with dupilumab. Data on dupilumab's safety is limited by the short follow-up time in most trials and the relatively low number of patients treated to date. Keeping those limitations in mind and based on current best evidence, it appears that dupilumab may enhance innate immune function in patients with AD.

J Drugs Dermatol. 2020;19(2)209-210. doi:10.36849/JDD.2020.4722

Atopic dermatitis (AD) is a chronic, immune-related, inflammatory skin disease that significantly reduces quality of life. In severe AD, systemic immunosuppressants (which inhibit the immune system's ability to fight infections and malignancy)— such as prednisone, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil— are often utilized, though they do not target specific biologic pathways of AD, and their long-term use is limited by moderate efficacy and adverse events.[1] Narrower, better targeted, non-immunosuppressive treatment may offer the possibility of high efficacy with better safety.

The underlying immune mechanisms of AD are becoming better understood. Interleukin 4 (IL-4) and IL-13 play key roles as evidenced by the genes for these signaling proteins being linked to AD. Dupilumab, the only FDA-approved biologic for AD (approved for adults and adolescents 12 and older), is a fully human monoclonal IgG4κ antibody that inhibits IL-4 and IL-13 signal transduction by binding to the shared α subunit of the IL-4 and IL-13 receptors.[2]

AD is a risk factor for *Staphylococcus* infections.[3] Dupilumab *reduces* the incidence of skin infections and eczema herpeticum in adults with moderate-to-severe AD by over 50%.[4] While this might be related to an improvement in the skin barrier integrity due to decreased scratching, dupilumab also changes the cutaneous microbiome, even in non-lesional skin, with a reduction in *Staphylococcus* density and an increase in microbial diversity.[2] Furthermore, IL-4 reduces antimicrobial peptide (AMP) production in the skin, which is a key component of the innate immune system.[5] Combining these observations suggests that the decrease in cutaneous *Staphylococcus* caused by dupilumab could be due in part to increased AMP production triggered by IL-4 blockade.

In a population-based claims data study of patients with AD, the incidence of serious infections was 7.5 per 1,000 (7.18-7.89) among systemic non-biologic users compared to 2.6 per 1,000 (0.45-14.3) among dupilumab users.[1] To date, no study has reported reactivation of latent infections (such as hepatitis B or tuberculosis, invasive fungal infection or unusual opportunistic infections) or progression of malignancy in association with dupilumab.

In conclusion, there is no evidence that dupilumab has immunosuppressive effects. On the contrary, by decreasing *Staphylococcus* colonization and partially normalizing the skin microbiome, likely via direct effects on the innate immune system, dupilumab appears to improve immunologic protection against infections. Data on dupilumab's safety is limited by the short follow-up time in most trials and the relatively low number of patients treated to date. Keeping those limitations in mind and based on current best evidence, it appears that dupilumab is not an immunosuppressant and the substantial decrease in infection rates makes it reasonable to say that dupilumab may enhance innate immune function in patients with AD.

DISCLOSURES

Steven R. Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate, and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Matthew Zirwas has received research, speaking and/or consulting support from a variety of companies including Abbvie, Aerolase, Aclaris, Aructis, Asana, AsepticMD , Avillion, DS Biopharma, Fit Bit, Foamix, Genench / Novartis, Incyte, Janssen, L'Oreal, Leo, Lilly, Menlo, Ortho Derm, Pfizer, Regeneron / Sanofi, and UCB. Adrian Cuellar-Barboza has no conflicts to disclose.

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