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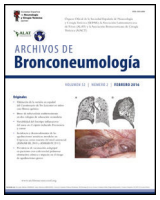

Editorial

Multiple Targets, Multiple Pathways, Multiple Strategies in the Treatment of Asthma

Biological response modulators, or 'biologics', have revolutionized the treatment of numerous immune-mediated diseases in recent decades. They act on the immune system by regulating target cytokines, membrane receptors and other key points of the immune response pathways involved in these disorders.[1] Around 175 biologics are currently approved or in regulatory review and nearly 1200 more molecules are under study, of which around 140 are already in late-stage clinical studies. Up to 20 new monoclonal antibodies came on the market last year in either the United States or Europe, and 24 more are pending regulatory approval. Although most of these immunoregulatory molecules have cancer indications, there is significant development in other areas, such as metabolic and infectious diseases, in which immunity plays an important role.[2] Patients with chronic immune-mediated diseases generally have very significant clinical responses to these drugs, but usually require lifelong treatments. Moreover, several diseases share a common immune-related pathophysiology, so some of these treatments may have different target populations, and the frequent presence of comorbidities in patients with chronic disorders may mean that a certain biological treatment can be used for two of these entities. In parallel, modulating a single immune system target may not be sufficient for adequate disease control. Finally, two immune-mediated entities may coexist, each requiring different biological treatments. Therefore, it is reasonable to consider the possibility of combining some of these biological therapies in a personalized approach.

The development of these therapies has not only increased the number of therapeutic targets, but their specificity and safety have also been improved in recent years by replacing murine-derived antibodies with humanized or fully human antibodies. This has reduced the likelihood of the immune system recognizing these proteins as foreign and generating an immune-mediated response against them.[3] Biologics are large, highly specific molecules, and are therefore unlikely to interact with other drugs; additionally, due to their pharmacokinetics and pharmacodynamics, they have a long half-life, which is an advantage for dosing.[1] Adverse effects are rare, the most common being various immune reactions (overstimulation, hypersensitivity, cytokine or immune imbalance, and cross-reactivity), although some effects not directly related to immunity have also been reported,[4] such as progressive multifocal leukoencephalopathy, prothrombotic changes, malignancy and cardiotoxicity.[5] Undesirable immune-related effects are particularly important, since these therapies are indicated in diseases involving immune-inflammatory system dysfunction, and therefore unexpected adverse reactions may occur. Immunosuppression, especially in antibodies that modulate key immune system pathways, such as those related to defense against infection or cancer, is another side effect to be aware of, as it can lead to serious infections. In fact, the risk of infection increases with the combination of two of this particular type of biological treatment, and there is sufficient evidence to advise against certain combinations, such anti-TNF drugs (for example, certolizumab) plus abatacept (T-cell blocker), anakinra (IL1 receptor antagonist), rituximab (anti-CD20) or natalizumab (anti-integrin α4).[6] Combinations that act on less central immune pathways have a much milder impact.

With respect to asthma, the emergence of new monoclonal antibodies in the past 5 years has revolutionized the treatment of patients with T2 asthma, a phenotype in which both the innate and adaptive systems responsible for the release of inflammatory cytokines (IL5, IL4, IL13, TSLP) and IgE are activated.[7] These mediators are found in pathways less involved in fighting viral and bacterial infections and responding to tumors. Drugs that block them (directly or through their receptors, or 'R'), such as omalizumab (anti-IgE), mepolizumab and reslizumab (both anti-IL5), benralizumab (anti-IL5R), dupilumab (anti-IL4R/IL13) and tezepelumab (anti-TSLP), have demonstrated good effectiveness, with improvements in the exacerbation rate, asthma control and lung function. Although there are no long-term studies (except for omalizumab), the safety data are reassuring, as the rate of serious adverse events is low or very low in all of them. In fact, the most frequent adverse effects are pain at the injection site and general malaise.[8]

There are almost no publications on biological therapy combinations that can be used in the treatment of asthma or other diseases with pathophysiological components linked to immunity. Fougerousse et al. published the largest case series, with 10 patients receiving biotherapy comprised of omalizumab for a dermatological indication in combination with other biological drugs for various associated entities (with an anti-TNF in nine patients, and an anti-IL17A in the remaining patient), with a mean follow-up of 41 months. The authors reported good effectiveness, with no serious adverse effects.[9] Another smaller series reported three patients with asthma and associated rheumatological diseases, demonstrating that the combination of two drugs (mepolizumab–etanercept, omalizumab–infliximab and omalizumab–etanercept, respectively) obtained a good clinical response in both entities, with no adverse effects.[10] A review

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recently published on combination biologic use in different diseases details the 45 cases published in patients with asthma, most of which are case reports or conference communications. In most cases, combinations of two drugs indicated for asthma were used, with a follow-up of 4 months to 4 years. The combinations were well tolerated, and only one minor adverse effect was described (conjunctivitis in relation to dupilumab).[6]

Our own experience consists of six patients: four treated with an anti-TNF drug (two with mepolizumab–etanercept, one with benralizumab–golimumab, and the other with benralizumab–adalimumab) and two with an anti-CD-20 (mepolizumab–rituximab). Follow-up was between 8 and 27 months and the combination was well tolerated, with no adverse effects observed.[11]

Although more data and larger series are needed, we should be aware that many of the new biological therapies are emerging as therapeutic options for one or several diseases, and their mechanisms of action can be considered complementary in many cases. This means that we will ultimately be faced with the dilemma of whether or not to prescribe an additional biological treatment in a patient with difficult-to-control asthma who is already receiving one of these therapies. The published evidence so far is scarce, and real-life experience needs to be combined with data from multicenter registries. Nevertheless, the results published to date suggest that combining biological drugs may be a reasonable option if they have a very specific mechanism of action and little ability to modulate critical pathways of the immune system, as is the case with the monoclonal antibodies used for asthma. If they are administered, it would be prudent to do so separately, taking into account the half-life of each drug, and to closely monitor them with special attention to the onset of adverse effects.

Conflict of Interests

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2023.07.032.

References

1. Foltz IN, Karow M, Wasserman SM. Evolution and emergence of therapeutic monoclonal antibodies: what cardiologists need to know. Circulation. 2013;127:2222–30.
2. Kaplon H, Crescioli S, Chenoweth A, Visweswaraiah J, Reichert JM. Antibodies to watch in 2023. MAbs [Internet]. 2023;15, http://dx.doi.org/10.1080/19420862.2022.2153410.
3. Patel SV, Khan DA. Adverse reactions to biologic therapy. Immunol Allergy Clin North Am [Internet]. 2017;37:397–412, http://dx.doi.org/10.1016/j.iac.2017.01.012.
4. Hausmann OV, Seitz M, Villiger PMPW. The complex clinical picture of side effects to biologicals. Med Clin North Am [Internet]. 2010;94:791–804, http://dx.doi.org/10.1016/j.mcna.2010.03.001.
5. Banker DD. Monoclonal antibodies. A review. Indian J Med Sci. 2001;55:651–4.
6. Quiroga LC, Sabourin AA. Review of dual biologics in specialty pharmacy practice. Ann Pharmacother. 2023;57:1094–110.
7. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell [Internet]. 2021;184:1469–85, http://dx.doi.org/10.1016/j.cell.2021.02.016.
8. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C, Canonica GW, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy. 2020;75:1023–42.
9. Fougerousse AC, Becherel PA, Pallure V, Boyé T, Reguiai Z, Gabison G, et al. Combining omalizumab with another biotherapy. Acta Derm Venereol. 2019;99:448–9.
10. Malik M, Jones B, Williams E, Kurukulaaratchy R, Holroyd C, Mason A. Dual biologic therapy for the treatment of rheumatic diseases and asthma: a case series. Rheumatol Adv Pract. 2022;7:4–6.
11. Navarrete Rouco ME, Carballo N, Bobolea I, Martínez-Moragón E, Pascual S, Labrador M, et al. Dual Biologic therapy – is it safe in patients with concomitant severe asthma and other immune-mediated diseases? Eur Respir J. 2022;60 Suppl. 66:3970.

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