SHORT COMMUNICATION

Combining Omalizumab with Another Biotherapy

Anne-Claire FOUGEROUSSE[1], Pierre-André BECHEREL[2], Valérie PALLURE[3], Thierry BOYÉ[4], Ziad REGUIAI[5], Germaine GABISON[6], Hughes BARTHELEMY[7], Antoine BADAOUI[8], Emmanuel MAHÉ[8] and Cristina BULAI LIVIDEANU[9]; for the GEM ResoPso

Departments of Dermatology: [1]Military Teaching Hospital Bégin, 69 avenue de Paris, FR-94160 Saint Mandé, [2]Private Hospital of Antony, Antony, [3]Hospital Center of Perpignan, Perpignan, [4]Military Teaching Hospital Sainte-Anne, Toulon, [5]Courlancy Polyclinic, Reims, [7]Hospital Center of Auxerre, Auxerre and [8]Victor Dupouy Hospital Center, Argenteuil, [6]Dermatology practice, Saint-Maurice, and [9]Paul Sabatier University, CReference Center of Mastocytosis (CEREMAST); Department of Dermatology, Toulouse Teaching Hospital, Toulouse, France. E-mail: ac.fougerousse@gmail.com

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Our improved understanding of the chronic inflammatory diseases has enabled the development of biologics, targeting multiple pathways, such as tumor necrosis factor (TNF), interleukin (IL)-23, IL-17, IL-1, or the receptor activator of NFκB ligand (RANKL), with new indications and biologics constantly emerging. Depending on the pathogenesis of the disease being treated, combination of biologics can target the same or two different pathways, resulting in different safety profiles.

Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, has been approved for the management of chronic asthma and chronic spontaneous urticaria (CSU), refractory to H1-antihistamines (1). While its sequential combination with other biologics has already been reported (2), the combined use with another biotherapy has only been reported once (3).

This retrospective study, involving the GEM Resopso centers, conducted between May 2017 and March 2018, sought to investigate the safety and efficacy of combined biotherapy comprising of omalizumab, dermatologically indicated, and another biologic medication prescribed for dermatological, rheumatological or gastrointestinal indications. The inclusion criteria were: disease diagnosis according to the current guidelines (4); age >18 years; combined omalizumab and another biologic therapy for ≥3 months. Patients' age, sex, underlying disease diagnosis, biotherapy type and duration, CSU disease evolution, CSU disease progression since omalizumab initiation, and adverse events were collected.

The study included 6 women and 4 men, with a mean age of 37.6 years (range 21–60) . The biotherapy indication was dermatological (psoriasis) in 7 patients, gastroenterological in 2 patients (Crohn's disease and ulcerative colitis), and rheumatological (ankylosing spondylitis) in one patient (**Table I**). Omalizumab was combined with biologics, such as anti-TNF agents in 9 patients and secukinumab in one, with a mean of 40.8 months (range 6–108) of treatment duration. In 9 patients, the indication for omalizumab was CSU, after failure to respond to the antihistamine dose increase; the remaining omalizumab-receiving patients suffered from indolent systemic mastocytosis with idiopathic anaphylactic shocks over 132 months. In all 10 patients, omalizumab was initiated after the first biologics, with combined biotherapy duration of a mean of 7 months (range 3–12). The initial biotherapy was pursued in all patients, except for one female patient, who was switched to ustekinumab, following an inadequate psoriasis control by adalimumab. Clinical response to omalizumab proved significant in all but one patient. In 8 CSU patients, complete clinical response, i.e. Urticaria Activity Score (UAS) 7 equal to zero, was achieved with omalizumab and a partial response in one, defined by a 30% decrease in UAS 7. This patient, however, discontinued antihistamines during observation. With omalizumab, the patient suffering from systemic indolent mastocytosis stopped experiencing idiopathic anaphylactic shocks. The combined biotherapy was well tolerated, with omalizumab producing no adverse

Table I. Patient and disease characteristics

Patient	Age, years/ Sex	Biotherapy indication	Biotherapy type	Biotherapy duration, months	CSU duration, months	Omalizumab treatment duration, months
#1	28/F	Psoriasis	Secukinumab	6	12	3
#2	35/F	Psoriasis	Adalimumab	9	24	8
#3	25/F	Psoriasis	Adalimumab	64	84	9
#4	21/F	Crohn's disease	Infliximab	18	12	4
#5	29/M	Ankylosing spondylarthritis	Etanercept	48	60	9
#6	60/F	Psoriasis	Infliximab	72	24	3
#7	25/M	Ulcerative colitis	Adalimumab	10	10	7
#8	51/M	Psoriasis	Etanercept	36	144	10
#9	49/M	Psoriasis and psoriasis arthritis	Etanercept	37	NA	12
#10	53/F	Psoriasis	Etanercept	108	2	12
	Mean 37.6	Gastrointestinal: 2 Dermatology: 7 Rheumatology: 1	ETN: 4 IFX: 2 ADA: 3 SECU: 1	40.8	41.3	7

CSU: chronic spontaneous urticaria; ETN: etanercept; IFX: infliximab; ADA: adalimumab; SECU: secukinumab; NA: not available.

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events when added to the existing biotherapy. None of the patients required hospital admission for any reason.

Patients with CSU are at risk of autoimmune diseases such as Hashimoto's thyroiditis, pernicious anemia, vitiligo, diabetes mellitus type 1, Grave's disease, coeliac disease, and rheumatoid arthritis (5). Combining omalizumab with biologic drugs of different mechanism of action, should not be associated with beneficial or detrimental interactions, however data is limited. Concerning omalizumab, the most common reported adverse events were headache, asthenia, myalgia, and injection-site reactions (6). Regarding anti-TNF agents, the most frequently observed adverse events were bacterial infections and local injection-site reactions (7). In our series, neither infections nor local reactions were noted. This was also the case in combining omalizumab and etanercept for one patient with CSU and rheumatoid arthritis (RA) (3).

Biologics, targeting different pathways, such as denosumab (a humanized monoclonal antibody that binds to RANKL, improving osteoporosis) and anti-TNFs, do not increase adverse events, such as infection rates in RA (8). In RA, however, using abatacept (a selective co-stimulation modulator), combined with biologics (9) or etanercept with anakinra (a selective anti-IL-1 agent) (10) caused an increased rate of serious adverse events. When combining biologics, physicians must take in account the profile of tolerance for each one, in order to avoid the detrimental interaction (e.g. risk of infection).

In conclusion, this observational approach of combining omalizumab with other biologics demonstrated encouraging safety and efficacy data. Registry studies could help to collect more information on this subject.

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