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Sequential Combined Therapy With Omalizumab and Rituximab: A New Approach to Severe Atopic Dermatitis

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■ **Abstract**

Background: Atopic dermatitis (AD) is a common chronic skin disease, and a significant percentage of AD patients have severe forms. Inflammation based on type 2 helper T cells (T_H2), autoantibodies, and CD8+ T cells could play a relevant role in this disease. When the patient requires systemic immunosuppressors for disease control, side effects are frequent. We propose a sequential therapeutic strategy with 2 monoclonal antibodies, omalizumab (anti-immunoglobulin [Ig] E) and rituximab (anti-CD20), which might induce clinical benefit with few side effects in selected individuals with AD.

Methods: We report 6 cases of severe AD refractory to conventional therapy. The patients underwent sequential switch therapy with omalizumab and rituximab . Clinical response was assessed by means of the decrease in body surface affected. Immunological parameters and side effects were also monitored.

Results: Four patients received omalizumab before a high-dose cycle of rituximab. In the case of recurrences, either low-dose cycles of rituximab or omalizumab were administered. A long-term clinical benefit was observed in 3 out of 4 patients. Two patients first received high-dose rituximab followed by either low-dose rituximab or omalizumab, and one of them achieved a response at 17 months. No severe side effects were recorded. Serum IgE level and B-cell counts decreased with therapy, the latter returning to baseline levels 10 to 11 months after treatment. Specific antibody responses remained protective during the study.

Conclusions: With our proposed switch therapy, 4 out of 6 patients achieved a dramatic clinical improvement. This novel strategy targets different arms of the immune response and might be a good alternative for patients with severe AD.

Key words: Atopic dermatitis. Omalizumab. Rituximab. Autoimmunity. Allergy.

■ **Resumen**

Antecedentes: La dermatitis atopica (DA) es una enfermedad crónica de la piel. En un porcentaje elevado de pacientes con formas graves de DA, es problable que existan autoanticuerpos y linfocitos T CD8+ actuando junto con células Th2 en la fisiopatología. En los pacientes que requieren inmunosupresores sistémicos para controlar la enfermedad, los efectos adversos son frecuentes. En este trabajo proponemos la administración secuencial de dos terapias con anticuerpos monoclonales (omalizumab, anti-IgE y rituximab, anti-CD20) como estrategia terapéutica eficaz con un grado aceptable de efectos adversos.

Métodos: Presentamos 6 pacientes con DA grave y recalcitrante a inmunosupresores convencionales que recibieron terapia secuencial con omalizumab (Xolair®)/Rituximab (MabThera®). La respuesta clinica se evaluó mediante la variación en la superficie corporal afectada. Se monitorizaron parámetros inmunológicos y efectos adversos.

Resultados: Cuatro pacientes recibieron omalizumab seguido de un ciclo de alta dosis de rituximab (HR). En las siguientes recaidas se administró un ciclo de baja dosis de rituximab (LR) u omalizumab. Tres de los 4 pacientes consiguieron mejoría clínica prolongada. En 2 pacientes se administró primero HR seguido o bien por LR, o por omalizumab. Uno de ellos consiguió remisión durante 17 meses. No se

registraron efectos adversos graves. La IgE y las células B sericas disminuyeron tras la terapia; estas últimas no recuperaron su nivel basal hasta 10-11 meses después. Las respuestas específicas de anticuerpos permanecieron en niveles protectores durante el estudio.

Conclusiones: Con esta terapia, 4 de los 6 pacientes con DA grave consiguieron una mejoría significativa. Esta estrategia se dirige específicamente a varios mecanismos efectores del sistema inmunológico y podría ser una alternativa para un grupo seleccionado de pacientes con DA grave.

Palabras clave: Dermatitis atópica. Omalizumab. Rituximab. Autoinmunidad. Alergia.

Introduction

Atopic dermatitis (AD) is a recurrent inflammatory skin disorder. Acute AD is characterized by erythematous and exudative lesions, whereas the chronic form is characterized by lichenification and crusting [1]. As with any other atopic disorder, AD is associated with tissue infiltration by type 2 helper T cells (T_H2) and immunoglobulin (Ig) E–producing B lymphocytes, eosinophils and their mediators, mast cells, and basophils [2]. In AD lesions, antigen-presenting cells and other inflammatory cells express increased amounts of the high-affinity IgE receptor FcεRI, which triggers IgE-facilitated antigen presentation [3]. Importantly, B cells from atopic patients have recently been shown to promote T_H2 polarization of naïve T cells [4].

This T_H2-driven inflammation is predominant in acute AD lesions [2]. However, in the chronic form of the disorder, T_H17 and T_H1 cytokines (interleukin 17 and interferon γ, respectively) and tissue remodelling factors (transforming growth factor β) coexist with eosinophil mediators and FcεRI+ cells [5]. Most AD patients have high levels of serum IgE, which can target allergens, microbial antigens, and skin autoantigens [6]. Although IgE autoantibodies are not associated with clinical manifestations, some authors considered that autosensitization might be indicative of effector mechanisms other than IgE (autoreactive IgG-producing B cells or CD8+ cells) playing a role in T_H17/T_H1–associated forms of AD [7,8]. Interestingly, IgE autoantibodies are more prevalent in severe and chronic forms of AD than in milder ones [9]. Taken together, these phenomena link allergy to autoimmunity and pave the way for novel therapeutic strategies.

As our understanding of immune dysregulation of AD increases, new immunomodulatory drugs other than systemic corticosteroids and classical immunosuppressors are emerging [10]. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody approved for some types of bronchial asthma, has been shown to downregulate FcεRI expression on cells and to decrease free IgE and inhibit eosinophil chemotaxis to tissues [11]. It has been used for several diseases on the atopic spectrum, including AD. According to data obtained from bronchial asthma trials, the beneficial effect of omalizumab is achieved only after several months of therapy [12].

Rituximab, a chimeric monoclonal antibody that binds specifically to the CD20 antigen present on the surface of B cells [13], produces B-cell depletion via induction of apoptosis. Although approved only for Hodgkin lymphoma and rheumatoid arthritis (prototypical T_H1 disorder), rituximab has been successfully used for several autoimmune T_H17/T_H1– and

T_H2-mediated diseases [14-16]. Consequently, B cells from patients with severe AD could be targeted successfully by rituximab. This drug is administered according to approved schedules and acts quicker than other therapies [17].

We propose a synergistic approach based on the pathogenesis of AD, namely, sequential combined switch treatment consisting of omalizumab and rituximab.

Materials and Methods

Design

The aim of this single-center, observational study was to describe the clinical effect and safety profile of sequential therapy with omalizumab and rituximab in a series of patients with AD that was refractory to conventional approaches. The inclusion criteria were as follows: *(1)* A diagnosis of AD made by an allergist or dermatologist according to current guidelines [18]; *(2)* Persistent eczematous lesions on >50% of the body surface for the last year despite cotreatment with high-dose oral corticosteroids (OCs: 1 mg/kg/day prednisone) plus 1 or more systemic immunosuppressors for at least 6 months during this period; and (3) age >20 years.

Before beginning treatment, all patients were informed about off-label use of these drugs and their safety profile. All patients signed the informed consent. During the study, patients were followed by a multidisciplinary team of physicians including a dermatologist, allergist, and clinical immunologist.

Patients

The study population comprised 6 white patients who were included between 2006 and 2010 (mean [SD] age, 36.0 [5.8] years). They had had AD from childhood, and their disease had deteriorated in the form of persistent lesions on >50% of the body surface during the years before the study (2.7 [1.0] years). During the previous 2 years, flare-ups (increase to >75% of body surface affected) had a mean duration of 10.4 (9.1) months/episode. Before the study, the patients had tried multiple sequential therapeutic lines other than OCs (Table). All patients were unresponsive to high-dose oral ciclosporin (5 mg/kg/day; mean duration of treatment, 10 months [range, 2-24 months]), and 3 of the 6 had also tried high-dose oral methotrexate (50 mg/week; mean duration of treatment, 3 months [range, 1-6 months]) with no effect. Four of the 6 patients had been admitted to hospital with a relapse of AD for more than 1 week during the previous 2 years. At the moment of inclusion, all of them had been receiving exclusively high-

Table. Epidemiological and Clinical Features of Our Series of Patients With Severe Atopic Dermatitis[a]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, y (sex)	33 (female)	44 (female)	30 (male)	29 (female)	32 (female)	37 (male)
Other atopic conditions	BA, FA	ARC, FA	ARC, FA	ARC, BA, FA	ARC, BA, FA, LA	ARC, BA, FA
Psychiatric conditions	No	No	MD	–	MD (suicidal thoughts)	MD
AD clinical features	More intense on head	More intense on head and neck	More intense on head	More intense on head and neck	More intense on head	Equally distributed
Immunosuppressors received before the study	TCI, OCy, OA, PUVA	TCI, OM, OCy	OM, OCy, OA, OT, IVIG	OCy, OA, PUVA	TCI, OCy, OA, PUVA, SE	TCI, OCy, OM, PUVA
First intervention (cycles)	Omalizumab (1)	Omalizumab (2)	Omalizumab (2)	Omalizumab (2)	IC rituximab	IC rituximab
Response (mo)	Complete (7)	Partial (6)	Partial (24)	Complete (7)	Complete (6)	Partial (6)
Second intervention	IC rituximab	IC rituximab	IC rituximab	First dose IC rituximab	MC rituximab	MC rituximab
Response (mo)	Complete (7)	Complete (9)	Partial (11)	Partial (40)	Partial (4)	Complete (2)
Third intervention (cycles)	MC rituximab	MC rituximab	Omalizumab (1)	Not done	Omalizumab (4)	MC rituximab
Response (mo)	Partial (2)	Complete (1)	Absent		Complete (17)	Partial (2)
Fourth intervention (cycles)	MC rituximab	MC rituximab, omalizumab (2)	Not done		Not done	Omalizumab (1)
Response (mo)	Complete (9)	Complete (31)	–	–	–	Absent
Fifth intervention (cycles)	Omalizumab (1)	Not done	–	–	–	Not done
Response (mo)	Complete (10) and partial (5)	–	–	–	–	–
Side effects	Urinary and respiratory tract infections	No apparent side effects	No apparent side effects	No apparent side effects	Type III anaphylaxis to rituximab; urinary tract and skin infections	Mononucleosis and neutropenia

Abbreviations: ARC, allergic rhinoconjunctivitis; BA, bronchial asthma; FA, food allergy; IC, induction cycle; IVIG, intravenous immunoglobulin; LA, latex allergy; MC, maintenance cycle; MD, major depression; OA, oral azathioprine; OCy, oral ciclosporin; OM, oral methotrexate; OT, oral tacrolimus; PUVA, psoralen UV-A therapy; SE, systemic efalizumab; TCI, topical calcineurin inhibitors.
[a]Responses are shown as they were 3 months after starting the omalizumab/rituximab ICs and 2 months after initiating rituximab MCs. Duration of response

dose OCs for the previous 4 months and had experienced side effects. All the patients had very high mean (SD) baseline levels of total serum IgE (tIgE) (12 300 [8288] IU/mL), but none of them fulfilled the National Institutes of Health criteria for hyper-IgE syndrome [19]. All the patients reported impaired quality of life, and 3 out of 6 patients had been diagnosed with major depression and were taking psychotropic drugs. Patients had multiple atopic comorbidities (Table) but no other significant disease.

Switch Therapy Protocol

Drugs

Anti-IgE therapy: Omalizumab (Novartis SA) was administered in cycles of 450 mg/2 weeks for 3 months (the highest dose recommended by the manufacturer for bronchial asthma).

Anti-CD20 therapy: All patients underwent full-body CT scans before starting rituximab (Roche SA) in order to rule

out the presence of occult neoplasm. Patients were scheduled to receive 2 types of cycle according to the protocol approved for Hodgkin lymphoma, namely, an induction cycle (IC) (4 weekly intravenous infusions at a dose of 375 mg/m^2 of body surface area) or a maintenance cycle (MC) (2 infusions of 1 g separated by 2 weeks).

Protocol

Patients with lesions affecting 50% to 75% of body surface were programmed to begin with omalizumab. The clinician could decide between prescribing 1 or 2 cycles depending on clinical outcome. On the first relapse, a rituximab IC was administered. For subsequent flare-ups, either a rituximab MC or cycle of omalizumab was administered (depending on the pattern of previous responses and baseline disease).

Patients with lesions affecting >75% of body surface were scheduled to start with a rituximab IC in order to attain a quicker effect. On the first and second recurrences, they received a rituximab MC; subsequent flare-ups were treated with omalizumab.

The prescribing physician changed or withdrew the drugs in the absence of response to any cycle.

Cotreatment During the Protocol

Topical treatments: Patients were allowed to use topical corticosteroids (0.1% methylprednisolone) once a day based on their own criteria. Skin care measures including topical emollients were also continued.

Systemic treatment: When patients developed a relapse during the study they received a 1-week cycle of OC (maximum of 1 mg/kg/day of prednisone), together with the corresponding biological. No other medical or physical treatment was allowed during the protocol, except for psychotropic drugs.

Outcomes

Clinical outcomes: If the body surface affected decreased to <20% after initiating the first switch therapy, OCs were progressively tapered until discontinuation over 3 months. Patients who were able to stop continuous intake of OCs and maintain the clinical improvement were classified as responders. If this objective was not met in the 3 months after starting each intervention, the patient was considered a nonresponder.

Patients on switch therapy were classified as complete responders if they did not need any other systemic therapy to achieve <20% body surface affected. Patients were classified as partial responders when they needed high-dose OCs for a maximum of 1 week not more than once a month to achieve <20% body surface affected. Patients who had previously responded to therapy and who started needing OC more than 1 week/month to maintain <20% of their body surface affected were considered nonresponders.

Safety: Adverse effects were carefully monitored in our day hospital during each visit.

Immune Response

Subsets of blood lymphocytes were analyzed using

multiparametric flow cytometry at baseline and after treatment. Cells were labelled by direct staining with mouse antihuman conjugated antibodies (CD3, CD4, CD8, CD19, CD56, and CD16) using single platform analysis (TruCount/Multitest method, FACScalibur, Becton Dickinson) and CellQuest software. Levels of serum Ig were quantified by nephelometry. The specific antibodies (sAb) antitetanus toxoid antibody (anti-TT) and antipneumococcal antibody (anti-PCP) were quantified using sAb ELISA kits (The Binding Site) before and after treatment to assess the effect of the therapy on sAb responses.

Results

Cutaneous Response

Patients pretreated with omalizumab: In the 4 patients included in this group (patients 1-4), skin lesions started to decrease 2 months after initiating switch therapy, with maximum improvement from the third month of treatment onward. In 3 of the 4 patients (patients 2, 3, and 4), 2 consecutive cycles of omalizumab were administered in an attempt to attain a complete response (Table). These 4 patients achieved responses of 6-24 months after this first intervention. Subsequent rituximab ICs were administered in the case of recurrences.

In 1 female patient (patient 4), social problems forced her to discontinue the IC after the first infusion; nevertheless, she achieved a partial response with this single dose for 40 months.

The other 3 patients started to improve after the second infusion of rituximab IC (1 week after initiating the drug), and the maximum response was achieved 1 month after finishing the IC. All 3 patients responded to this second intervention and maintained their response for 7-11 months.

After the following 2 relapses (third and fourth interventions), rituximab MCs were administered to patients 1 and 2, followed consecutively by 2 cycles of omalizumab in patient 2. Patient 1 also received a cycle of omalizumab, although after 9 months of complete response. Both patients attained complete and sustained responses, with patient 1 being symptom-free for more than 2.5 years.

Patient 3 received a new cycle of omalizumab with the intervention owing to the more sustained response to this drug than to rituximab in previous attempts. No decrease in the extension of his lesions was achieved with this strategy.

Patients pretreated with rituximab: The condition of both patients (patients 5 and 6) started to improve 1 month after finishing the first intervention (8 weeks after initiating the rituximab IC). Both were responders for 5 to 6 months. Upon subsequent recurrence, both received an MC of rituximab and achieved a short response (4 and 2 months, respectively).

Patient 5 developed an anaphylactic reaction immediately after the second infusion of the MC, and a cycle of omalizumab was prescribed for possible subsequent flare-ups. The response was complete and sustained, and another 3 cycles of omalizumab were administered in order to maintain the clinical benefit. This patient has been symptom-free for 17 months.

Patient 6 received a rituximab MC on the second relapse with a short response. On the fourth intervention, omalizumab

was prescribed together with a 1-month cycle of oral ciclosporin (2.5 mg/kg/day maximum dose). The patient had several side effects and refused to take OCs. No benefit was obtained.

Other Clinical Parameters

Self-reported quality of life improved in all patients during treatment, mainly a decrease in pruritus. Moreover, 1 patient with major depression and suicidal thoughts was able to reduce the dose of psychotherapy and is now pregnant. No patients required admission to hospital owing to relapses of AD during the study.

Laboratory Results

We observed a marked reduction in total IgE measured at a mean period of 4.4 months (range, 2-6 months) after all cycles of switch therapy: pretherapy, 32 665.8 (52 868.3) IU/mL; posttherapy: 6882.6 (10 851.9) IU/mL. The remaining immunoglobulin isotypes decreased slightly, but not in the range of hypogammaglobulinemia (IgG pretherapy: 1142.2 [195.7] IU/mL; IgG posttherapy, 883.3 [165.0] IU/mL; IgA pretherapy, 206.0 [131.2] IU/mL; IgA posttherapy, 156.4 [102.9] IU/mL; IgM pretherapy, 120.7 [41.7] IU/mL; IgM posttherapy, 72.3 [13.2] IU/mL). Anti-TT and anti-PCP antibodies were maintained at protective levels (anti-TT, 4.55 [2.45] IU/mL; anti-PCP, 4.82 [1.90] mg/dL) for 2 years after rituximab ICs and MCs. Before starting rituximab therapy, the mean proportion of B cells in peripheral blood was 13.0% (1.2%) of total lymphocytes. In 4 out of 5 patients who completed the IC, $CD19^+$ (B cells) proportions remained undetectable for 6 months and did not return to normal levels until 10-12 months after cessation of rituximab therapy. No significant variation was seen in $CD3^+$ $CD4^+$ cells (helper T cells), $CD3^+$ $CD8^+$ cells (cytotoxic T cells), or $CD16^+$ $CD56^+$ cells (NK cells).

Safety Results

Rituximab was well tolerated in all patients but the one who developed the anaphylactic reaction (patient 5). Three of the 6 patients had infectious events due to therapy. Two patients developed frequent respiratory and urinary tract infections after starting rituximab, which in some cases led to new AD relapses. One of these patients (patient 5) required a short cycle of low-dose intravenous immunoglobulins and the other one (patient 1) a bacterial autovaccine. The most severe complication was seen in a patient who developed mononucleosis syndrome with severe neutropenia shortly after the IC of rituximab. He was admitted to hospital and responded quickly to granulocyte colony-stimulating factor (G-CSF filgrastim, Amgen Europe SA). He was discharged 5 days after admission. Omalizumab produced no apparent side effects when administered in monotherapy.

Discussion

Patients with AD whose disease is refractory to habitual immunosuppressors or who develop severe side effects must receive personalized treatment. Given the possible role of B

cells in autoantibody production and in T-cell costimulation seen in some severe forms of AD [9], we propose a new therapeutic strategy that targets not only inflammation mediated by IgE and FcεRI, but also T_H17/T_H1–based mechanisms (both cellular and humoral arms). Moreover, 5 out of the 6 patients in our series of refractory AD had predominantly head and neck lesions (Table); this pattern is associated with the presence of antibodies targeting fungal antigens (mainly Malassezia species) [20]. Cross-reactivity between some of these antigens (eg, antimanganese superoxide dismutase) and human skin proteins could be another possible mechanism of amplification of chronic inflammation in our series [21]. Based on the synergistic action of omalizumab and rituximab, we aimed to reset both arms of the immune system in this specific group of patients.

Administration of omalizumab to treat AD is the subject of debate. Although a blinded pilot study revealed a clinical benefit in acute forms [22], the several small series and single-case reports published [23,24] have shown conflicting data, and large-scale controlled trials are lacking. Unfortunately, the different doses and protocols used make results difficult to interpret. Evidence on administration of rituximab to treat AD is sparse, and the treatment schedules used in published studies are different to ours. In a 2008 series [25] of 6 patients with severe AD, a clinical response was observed in all patients between 4 and 8 weeks after starting therapy, as was an improvement in histological and laboratory parameters. Two intravenous infusions of rituximab (1 g, 2 weeks apart, as with the MC we used) were administered to all patients. Pilot studies are now in progress [26].

The clinical response to rituximab in patients pretreated with omalizumab in our study was faster than in other studies [25], possibly because of the higher dose of rituximab, neoadjuvant administration of omalizumab, or both. Interestingly, the patients pretreated with rituximab took 3 to 4 weeks longer to achieve a significant benefit than those pretreated with omalizumab, although the greater severity of the baseline lesions in the first subset could also have affected this response. All the patients showed some degree of clinical improvement with our strategy, and 4 maintained this benefit into the long term. Only 1 case series has reported benefits with other combined immunomodulatory therapies, including omalizumab plus intravenous immunoglobulin for severe AD [27]. Rituximab has also shown a beneficial effect on combination therapy with intravenous immunoglobulin for the treatment of pemphigus, a classic T_H2-driven disease [28]. The only reported combined use of omalizumab plus rituximab was for severe refractory insulin allergy [29].

Considering that induction of neutralizing antibodies is a frequent cause of loss of efficacy in long-term biological therapies [30], the ability of rituximab to impair the synthesis of antibodies, including neutralizing antibodies, could be another advantage of our strategy. The combined sequential therapy we propose might reset the immune response, not only to autoantigens, but also to the drugs administered.

Our regimen has a reasonable safety profile, and the doses prescribed during the study were much lower than those the patients had previously received. Biological therapies such as rituximab and omalizumab produce fewer side effects than

classic immunosuppressors (eg, systemic corticosteroids, ciclosporin, and methotrexate), possibly owing to a more specific and restricted action. Interestingly, single therapy with rituximab has been reported to be a safe option for AD during the first trimester of pregnancy [31].

Cost-effectiveness studies of biologicals in other immune-based diseases suggest that monoclonal antibodies are cost-effective in severe cases. The drugs administered in the day hospital in our study led to a marked clinical improvement in 4 of the 6 patients and, despite their high cost, they are still much less expensive than the cost of repeated hospitalizations, disability, work absenteeism, and lost productivity.

AD patients with an absent or nonsustained response to high doses of omalizumab might have a more complex disease than long-term responders to this drug, with the presence of T_H17/T_H1–driven inflammatory events involving mainly autoreactive IgG or CD8$^+$ T cells. In these cases, our proposed combined sequential therapy could lead to an omalizumab-induced decrease in expression of FcεRI on inflammatory cells and skin infiltration by eosinophils. This partial benefit might be complemented by rituximab-induced B-cell depletion that could produce a decrease in the synthesis of autoantibodies (of both IgE and IgG isotypes), B- and T-cell costimulation, and cellular hypersensitivity phenomena.

We propose combined sequential therapy with omalizumab and rituximab as an acceptably safe alternative for severe forms of AD where an autoimmune mechanism is suspected. Our approach is a new conceptual strategy that targets several arms of the immune response in a specific subset of AD patients.

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