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REVIEW

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Self-administration of omalizumab: why not? A literature review and expert opinion

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ABSTRACT

Introduction: Omalizumab is used to treat severe uncontrolled allergic asthma and chronic spontaneous urticaria (CSU), and is approved for self-administration in prefilled syringes. It is thus important to understand the advantages, critical issues, and indications for home administration.

Areas covered: The present review summarizes the available evidence on home administration of omalizumab in asthma and CSU to illustrate the advantages derived from self-administration of patients in this setting.

Expert opinion: The available data suggest that patients can safely administer biologics at home with suitable training, and that home administration is time saving and cost-effective. The majority of patients with severe asthma or CSU treated with omalizumab are likely to be suitable candidates for self-administration, which can be proposed to anyone that the clinician deems suitable. In addition to clinicians, pharmacists can also play a key role in managing patients who are prescribed home administration. A practical flow chart is proposed on selection of patients and their management during home administration. Self-administration of biologics can be considered as a valid alternative to traditional injections in a clinical setting, and the evidence has shown that no major issues need to be overcome in terms of safety or efficacy.

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1. Introduction

Self-administration, or home administration, of subcutaneous medications is routinely performed for patients with a variety of pathologies such as rheumatoid arthritis and diabetes. However, home administration of biologics has only recently become a therapeutic option for patients with respiratory diseases such as asthma. In reality, endocrinologists, rheumatologists, gastroenterologists, and dermatologists have had the opportunity to prescribe biological drugs for home injection for many years. The best-known example is insulin, of course, which has been used for almost 100 years and whose home self-management is consolidated and taken for granted [1]. Today, at least among those subcutaneously administered, many biotherapeutics used for rheumatoid arthritis, immunoglobulin-replacement therapy in primary immunodeficiency, and beta interferons in multiple sclerosis can be self-administered at home [2]. Despite this multidisciplinary experience, many pulmonologists and immunoallergologists are not routinely prescribing self-administration of biologic drugs for asthma. Accordingly, it is important to clarify the advantages, critical issues, and indications for home administration, in order to help clinicians facilitate their use.

Around 300 million people worldwide have asthma, and its prevalence continues to increase [3]. Severe asthma is present in 3.7% of asthma patients, and biologicals are the current treatment of choice in type 2 uncontrolled severe asthma [4]. Asthma and its treatment are thus global problems with significant impact on both clinicians and patients. Omalizumab, being one of five monoclonal antibodies approved by regulatory authorities for management of severe asthma (in addition to mepolizumab, reslizumab, benralizumab, and dupilumab), and being the first commercialized more than 10 years ago, is supported by a large body of evidence on the use of this monoclonal anti-IgE antibody as add-on therapy in uncontrolled asthma. Clinical trials have shown that omalizumab is well tolerated with a low incidence of side effects, comparable to placebo [5]. In the past, biologics used to treat severe asthma such as omalizumab were normally administered in a physician's office or medical clinic due to the supposed risk of anaphylaxis. However, studies have shown that the prevalence of anaphylaxis following subcutaneous injection with omalizumab in post-marketing use is only 0.09%, with the majority of these cases appearing during the first three injections [6,7]. This strongly suggests that the risk of anaphylaxis is low and should not be a limiting factor for home administration.

Omalizumab is also used to treat severe uncontrolled allergic asthma and chronic spontaneous urticaria (CSU). CSU has a prevalence of approximately 1% in the general population. CSU is characterized by the spontaneous

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Article highlights

- Omalizumab is approved for self-administration in prefilled syringes.
- The present review summarizes the available evidence on home administration of omalizumab in asthma and CSU to illustrate the advantages derived from self-administration.
- The available data suggest that patients can safely administer biologics at home with suitable training.
- Home administration is time-saving and cost-effective.
- The majority of patients with severe asthma or CSU treated with omalizumab are likely to be suitable candidates for self-administration.
- Pharmacists can play a key role in managing patients who are prescribed home administration.
- A practical flow chart is proposed on selection of patients and their management during home administration.

appearance of wheals, angioedema, or both for at least >6 weeks due to known or unknown causes [8,9]. Given its symptoms, CSU is a debilitating disease with substantial burden and a strong negative impact on the quality of life, interfering with sleep, work, and daily activities [10]. Treatment of CSU is also associated with significant costs and health-care resources [10]. Approximately 40% of patients do not respond to antihistamine therapy, even at high doses, and therefore are indicated for therapy with omalizumab according to EAACI/GA(2)LEN/EDF/WAO guidelines [9]. In clinical trials, omalizumab is associated with clinically significant outcomes and improvement in the quality of life [11].

In 2018, the European Medicines Agency (EMA) approved the use of omalizumab prefilled syringes for self-administration. At present, several other biologics for severe asthma have been approved for home administration, including mepolizumab, dupilumab, and benralizumab.

The availability of omalizumab and other biologics for home administration thus opens up new possibilities for patients to have greater independence in management of asthma and CSU. For example, it can be more convenient around employment schedules, for students, or those who have to travel long distances to the place where the injection is administered, with potential benefits on adherence and quality of life [12]. For healthcare providers, decreasing the number of patients requiring repeated courses of biologics has obvious consequences in terms of time saving and costs [12]. The same is true for patients having the possibility to self-administer their therapy at home, with potential benefits related with time and costs [12]. Important, the possibility to home administer a biologic should always be subject to the approval of the prescribing physician.

In spite of its potential positive impact, to date there are still few studies on published experiences with home administration of biologics in patients with severe asthma, and even fewer with CSU [13–16]. Notwithstanding, the available data suggest that patients can safely administer biologics at home with suitable training. The objective of the present review is to overview the available evidence on home administration of omalizumab in asthma and CSU to illustrate the advantages derived from self-administration and to provide practical guidance on selection and management of patients in this setting.

2. Omalizumab for asthma

2.1. Indications

In adults and adolescents over the age of 12 years, omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 < 80%) as well as frequent daytime symptoms or nighttime awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist [17]. In children 6–12 years of age, omalizumab is similarly indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or nighttime awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

Omalizumab treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma [17]. A recent study has shown that a large proportion of patients with severe allergic asthma have a blood eosinophils count ≥300 cells/μL and suggest that the effectiveness of omalizumab is similar in 'high' and 'low' eosinophil subgroups [18].

Dosing of omalizumab should be performed according to the guidance provided in the prescribing information [17]. Omalizumab is available as a pre-filled syringe solution for injection in 75 mg (0.5 ml) or 150 mg (1 ml) doses. For each subcutaneous administration, 75 to 600 mg of omalizumab in 1–4 injections may be required. The maximum recommended dose is 600 mg omalizumab every 2 weeks. Omalizumab is also indicated for long-term treatment, and for this reason, the doses must be adjusted in case of significant changes in the patient's body weight.

2.2. Administration technique

Administration of omalizumab is made subcutaneously. On the basis of the initial data on the risk of systemic reactions, reduced in subsequent administrations, it is still recommended to carry out the three first injections in a clinical setting. If the physician deems it appropriate, starting with the fourth administration, the self-administration regimen of omalizumab can be initiated after a careful evaluation of the patient's history of anaphylaxis, which should be done before proceeding with self-administration or receiving an injection from a caregiver. The patient or caregiver must have been instructed to use the correct injection technique and to

recognize the early signs and symptoms of any adverse event. Patients or their caregivers must have been instructed on how to inject the entire correct amount of omalizumab and then follow all the instructions in the package insert at home. Correct education is fundamental for all therapies and especially for biological agents: correctly instructing patients or those who take care of them reassures both patients and health-care providers on the safety and efficacy of the drug administered.

2.3. Benefits of home administration

Self-administration of biologics has the potential to be time saving for both patients and physicians as reported in a recent survey in Germany involving 120 physicians and 432 patients [12]. Roughly two-thirds of patients were in favor of home self-administration or had a neutral attitude. In addition, 76.7% of physicians favored home use for selected patients. Time saving was the most important benefit of self-administration cited by both patients and physicians.

In 2007, Liebhaber et al. reported their initial experience on 25 patients undergoing therapy with omalizumab, describing outcomes of 1,017 home therapy sessions administered during a 2-month to 4-year time period [16]. None of the patients reported a severe adverse reaction or anaphylaxis, and no patients required use of antihistamines or epinephrine. Importantly, all patients showed clinical improvement in symptoms of asthma. This was the first study to confirm that patients can safely and effectively self-administer omalizumab at home with appropriate precautions.

Shaker et al. carried out an economic microsimulation for patients with asthma or CSU treated with omalizumab or mepolizumab given at an allergy clinic, physician's office, or at home over a 1-year period of time with 12–24 injections per year [19]. Mean costs for administration in clinic were 1916.68 USD and 1369.14 USD for those in a physician's office, compared to 7.47 USD for home injection [19].

Home administration also has the potential to improve adherence, especially for patients living in areas with poor services, distant from hospitals and medical clinics, or geographically disadvantaged. Indeed, it has been estimated that the risk of a fatal traffic accident on the way to the clinic or physician's office is less than the risk of fatal anaphylaxis [20]. This helps to place the risk of home administration in context, and would decrease the overall costs of care.

2.4. Selection of patients for home or self-administration

First and foremost, clinicians should undoubtedly use their clinical judgment as to which patients should continue to be treated in the clinic and which patients would do well with home administration. Patient selection and an adequate educational training of patients or their caregiver before starting the home treatment is crucial. Evidence has shown that both patients and physicians have strong preferences for biologic agents in terms of less frequent dosing, subcutaneous administration, and faster onset of action [21]. Considering the administration route, a recent survey showed that there was an overwhelming preference by both patients (100%) and physicians (96%) for subcutaneous over intravenous injection [21]. In addition, among physicians who preferred home administration, patient administration was favored over caregiver administration. Considering this, physicians must work closely with patients to ensure that they are sufficiently informed, able to perform it correctly, and are willing to home administer omalizumab. Apart from this, we believe that all patients having the possibility to safely self-administer a biologic treatment should be offered the possibility to do so.

Simplicity of use, reliability and functionality of prefilled syringes and auto-injectors allows adequate home management with a low risk of critical errors by patients or caregivers or device malfunction [22]. Potential candidates for self-administration are those patients on school or working age, which are also the majority of those undergoing biologic therapy for severe asthma [23]. In addition, omalizumab is the only biological agent that can be used if clinically needed for treatment of asthma during pregnancy or breastfeeding based on approval received by the European health authority. Thus, if appropriate and clinically needed, all women of childbearing age can be treated with omalizumab [17], and it is thus likely that all would benefit from home administration.

Patients who are not suitable for self-administration are the elderly with neurological problems, those with a language barrier who are not able to understand physician indications, patients who are unreliable from the point of view of adherence, and patients with needle phobia without an available caregiver, or any patient with a personal preference to continue therapy at the asthma clinic [23].

There are other aspects to consider, which are the real adherence of the patients, the correct timing of administration, home drug storage and the management of adverse events. It is essential to maintain regular contact with patients, make regular visits and diagnostic tests to monitor the pathology (spirometry, exhaled nitric oxide, differential blood cell count).

The SARS-CoV-2 pandemic made it necessary to carry out a profound restructuring of the hospitals and outpatient organization in all areas [24]. During the pandemic or in the event of new pandemic waves, self-administration allows the reduction of hospital visits. In addition, home administration provides the opportunity for continuity of therapy without the need to drive to the clinic and expose themselves to potential infection with SARS-CoV-2. Moreover, in non-SARS-CoV-2 infected patients, a recent joint statement from ARIA the European Academy of Allergology and Clinical Immunology recommended that if the patient usually attends a hospital for biological treatments, training the patient to self-administer or treatment at a community clinic or home should be taken into consideration [25]. This is an advantage in terms of reducing the risk of possible contagion for patients and improves management for health-care providers, who are already heavily engaged and likely not able to regularly manage biologic asthma treatments for outpatients. In this regard, one could

envisage home delivery of biologics would be a substantial advantage to patients and further increase adherence to therapy.

Lastly, the role of the patient's general practitioner should also be considered, who has the ability to form a strong relationship with the patient and who should be informed about the mode of administration of a biologic drug.

2.5. Home self-administration in children

The efficacy and safety of omalizumab as add-on therapy in uncontrolled asthma have also been confirmed in children [26,27]. Since viral upper airway infections are the main trigger of asthma exacerbations in children [28], the burden of asthma exacerbations is very high in children, who are physiologically more prone than adults to recurrent respiratory infections [29]. Adolescents are a challenge when the correct management of asthma is at stake [30]. Psychological problems have also been reported in children with severe or persistent asthma [31,32]. When considering home administration of a biological drug, the reliability of the caregiver and, in general, the whole family should be taken into account. The same considerations given for adult patients also apply to children who will require administration by his/her parents or caregiver. The person giving the injection must receive proper education and be able and willing to provide reliable therapy.

3. Omalizumab in CSU

Omalizumab is prescribed as add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment [17]. The recommended dose is 300 mg by subcutaneous injection every 4 weeks.

Denman et al. evaluated the at-home self-administration of omalizumab for CSU, noting that the increasing number of patients requiring courses of omalizumab for CSU placed significant pressure on health-care staff [14]. In the cohort of 97 patients undergoing home administration with the longest treatment period of 70 months, there were no cases of anaphylaxis or other serious adverse effects in patients treated at home and no patient was subsequently transferred back to hospital. The authors also proposed a home-treatment pathway.

The same authors later described multicenter experience of home omalizumab treatment for CSU [33]. In total, the experience with 137 adult patients receiving home omalizumab treatment was described with a duration of 0–44 months. The authors reported no increase in adverse effects and no reported adherence issues. Moreover, it was noted that patients preferred home treatment given the increased flexibility and reduced impact on their daily life and employment.

Ghazanfar also reported their experience with home administration of omalizumab in 40 patients with CSU undergoing home administration for a median time of 2.8 years [34]. As with the above studies, there were no cases of anaphylaxis, allergic reactions, or serious adverse effects and no difference in safety issues between those treated in the clinic or by self-administration at home.

Given these positive experiences, the same positive considerations regarding the possibility of self-administration in severe asthma thanks to home administration also apply to patients with CSU. Home administration means that more time is available which can be used to treat patients with CSU who have more severe disease, who thus need more attention. Moreover, treatment interruption with biological agents is associated with an increased risk of immunogenicity and production of anti-drug antibodies that are associated with adverse infusion reactions [35]. The good safety profile of omalizumab and its low immunogenicity have also been confirmed in a real-life study performed in patients suffering from CSU, in which the repeated cycles after interruptions is not associated with adverse events in patients with CSU [36]. Taken together, these observations strongly support the self-administration of omalizumab at home.

In making the transition to home administration, it should be highlighted that first administration should be carried out by the medical/nursing staff accompanied by a step-by-step explanation of the subcutaneous injection. Next, during the second administration, the task can be divided: the first injection by medical staff with repetition of each step and the second by the patient or caregiver. In the third month of therapy, the third administration should still be carried out in a hospital setting, but can be carried out by the patient or caregiver under supervision of a physician/nurse. From the fourth administration onwards, the therapy can be performed at home. Patients are instructed to self-administer when they will be in the presence of another person for at least 2 h. A subsequent follow-up visit is scheduled after 3 months. At every visit, patients should inform medical staff about the date of the administration so that adherence to therapy can be verified. In any case, patients should be made aware that they can always contact the medical staff by phone or email.

4. Role of the pharmacist

When switching to home administration, the pharmacist supplies the drug to the patient with the possibility to have direct contact. This thus provides the possibility for the pharmacist to educate the patient or caregiver about key aspects that can help to minimize the risk of errors. This includes providing instruction on the correct storage of the drug and expiration date, give clarifications on the correct method of administration, recommending strict adherence to therapy and verifying that the patient fully understands the dosing scheme [21].

If one considers that the patient, once indicated for home use, in the absence of specific problems, will only return to the prescriber after a few months (generally 3 to 6 or in any case the time established by the clinician for adequate follow-up), the pharmacist can serve as another important reference point and source of information between one follow-up and the next. It is therefore important that the pharmacist query the

patient about possible problems in the management of therapy and drug (storage, method of administration, adverse effects, adherence).

The pharmacist can then intervene based on the type of problems encountered, either by providing clarifications directly to the patient, or by acting as an intermediary between the physician and patient in cases that require it or by interfacing directly with the specialist to report situations that require more in-depth evaluation.

An important aspect in which the pharmacist can intervene – if the patient always goes to the same pharmacy – is in monitoring adherence to therapy, a variable that with home use becomes fundamental for long-term effectiveness. Moreover, it should be suggested to patients that they should choose an easy-to-access pharmacy and, if possible, to always go the same one to facilitate monitoring of adherence. Assessment of adherence can be made by direct verification when the pharmacist provides the drug to the patient even simply by questioning and talking about the ongoing therapy. Indirectly, the pharmacist can also confirm the regularity and correct timing of previous dispensations, based on the former quantities supplied and the dosage and posology in the treatment plan. There are several specific applications that can support the pharmacist in monitoring this aspect. Lastly, the pharmacist can suggest the use of smartphone applications to the patient that can be useful to improve and control adherence to therapy.

The monitoring and optimization of this aspect, in which the role of the pharmacist becomes essential in the home use regime, also reduces the risk of negative economic impact due to a non-optimal efficacy and waste or misuse of the drug. A recent conference on the use of biologics stressed that pharmacists have key roles in the correct use of biological products, which may vary across practice settings [37]. In addition, the role of the pharmacist is decidedly evolving to adapt to new models of care such as home administration and can provide education about biologics and help monitor response to therapy. Indeed, it has recently been reported that pharmacists can have a major role in monitoring treatment plans and adverse events in biological treatment of rheumatological, gastroenterological, and dermatological pathologies [38]. Indeed, in patients with inflammatory bowel diseases, nonadherence to medication can be improved through pharmacist counseling [39,40]. Lastly, having a pharmacist involved in the clinical management of biological agents is believed to enhance the overall team model of patient care [41].

5. Conclusions

Based on the experience reported, self-administration of biologics for treatment of severe asthma and CSU can be considered as safe and efficacious as administration in a clinical or office setting. The available evidence, now spanning several years in some cases, indicates that many patients are willing and are satisfied with self-administration. It allows for more flexibility with busy work and social schedules, and avoids the need to come to the clinic on a regular basis. At the same time, with self-administration health-care providers achieve substantial time savings as they no longer need to administer the drugs to scores of patients on a regular basis. Prescribers can be confident about the lack of safety issues reported in any of the studies on use of omalizumab in a home setting. It is, however, important to make sure that patients are appropriate and willing to self-administer, and that they have been empowered to do so, also through adequate training, counseling, and education. Patients undergoing self-administration should also be adequately monitored and followed over time to ensure that the patient has no issues, and that efficacy is maintained. The patient's general practitioner, and whenever possible the patient's pharmacist, should be informed that the patient is self-administering so that they can serve as additional resources for the patient to refer to when clinical visits become less frequent.

6. Expert opinion

In our opinion, the majority of patients with severe asthma or CSU treated with omalizumab are likely to be suitable candidates for self-administration. Self-administration can be proposed to all patients that the clinician deemed suitable. As mentioned, the elderly with neurological problems, individuals with language barriers, those believed to be non-adherent, and those with needle phobia are not good candidates for self-administration, nor is any patient who maintains their personal preference to continue therapy in a clinical setting. Flow charts with guidance for establishing self-administration in patients with asthma or CSU are shown in (Figures 1 and 2), respectively. Patients should be considered for self-administration only after they have undergone 3 administrations in a clinical setting. The patient should be carefully counseled and the possible benefits explained, while listening to their impressions about self-administration and answering any questions. Patients should be reassured that they will receive adequate training and that support is always available from the treating clinic, as well as from their pharmacist and general practitioner. If the patient agrees to self-administer, both their pharmacist and general practitioner should be informed so that they can serve as additional points of reference for the patient. Lastly, during maintenance therapy, patients should still be followed on a regular basis in the clinic, even if the visits are less frequent, and it is still important to carry out diagnostic tests for efficacy and ensure that patient has no issues. If the patient is considered to be autonomous with no significant issues, then follow-up visits might be reasonably be made less often.

Self-administration of biologics can be considered as a valid alternative to traditional injections in a clinical setting, and the evidence has shown that there appear to be no major obstacles to overcome in terms of safety or efficacy. Self-administration has benefits not only for patients but also for health-care providers. Patient education must be considered as a fundamental component of rendering the patient autonomous, and patients must feel confident in their ability to self-

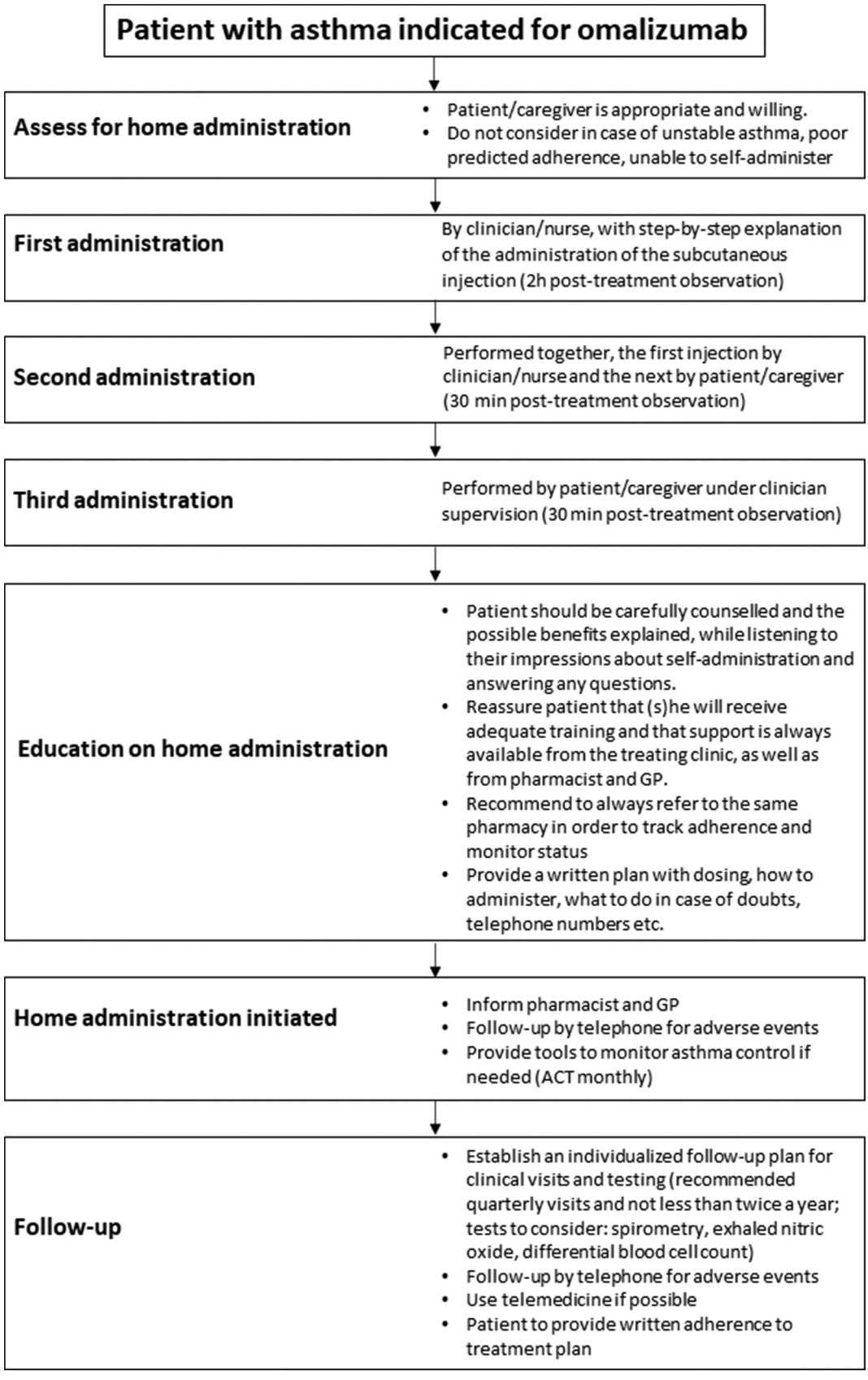

Figure 1. Flow chart for self-administration of omalizumab in patients with asthma.

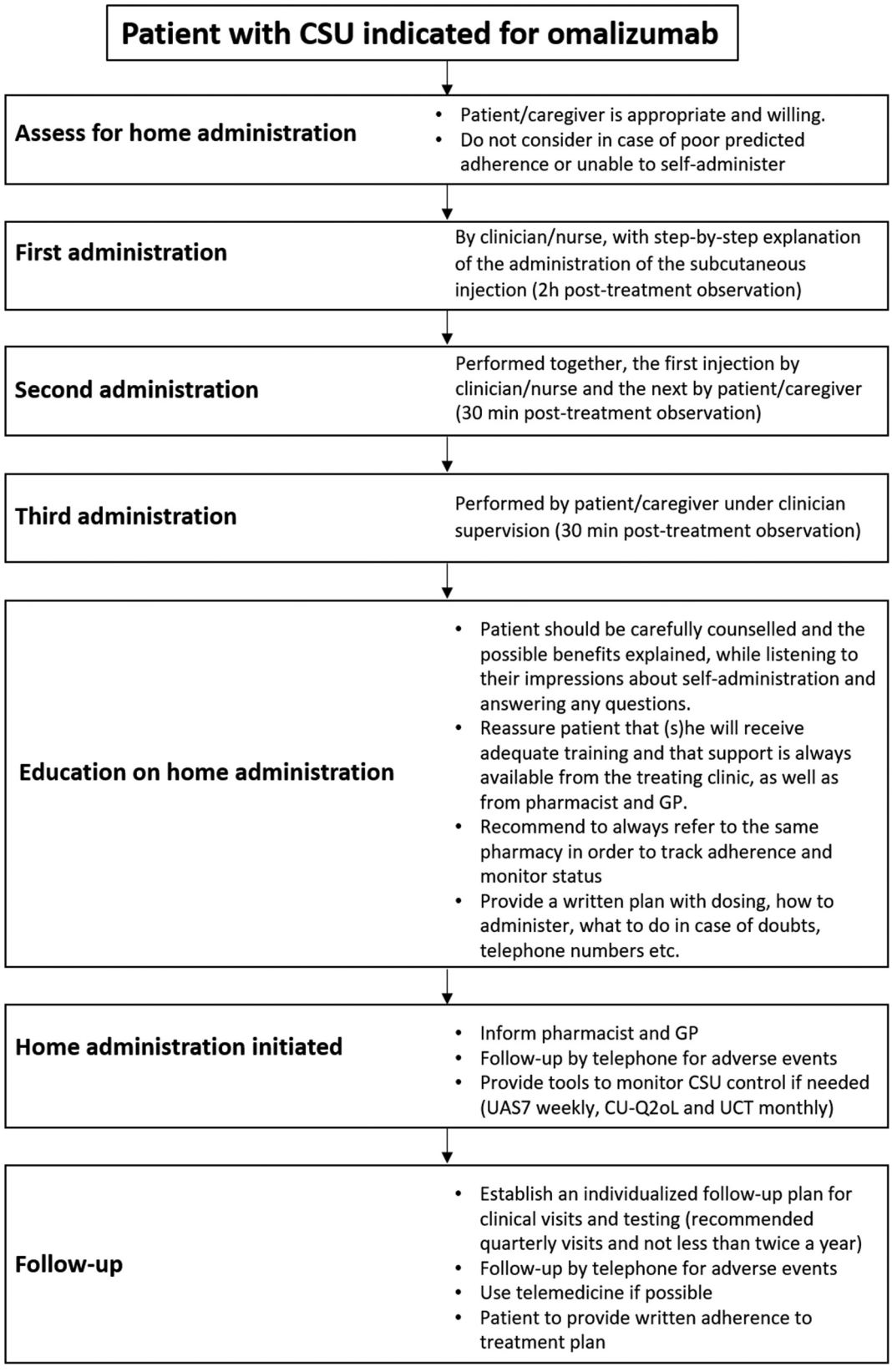

Figure 2. Flow chart for self-administration of omalizumab in patients with CSU.

administer. A feeling of empowerment will likely be associated with good adherence to therapy, and there are many tools that can help to monitor adherence. Moreover, patients must feel that they still have a valid support network in place with less frequent clinical visits, and involving pharmacists and general practitioners can help fill the gap in this regard.

At the same time, self-administration benefits health-care providers by giving them more time to dedicate to more pressing priorities. It will also lead to substantial cost savings that can be used for other necessities. Such savings are likely to be substantial considering the volume of patients who can self-administer the drug. As a word of caution, self-administration is appropriate for many patients, but not for all, and it should only be proposed to patients after careful evaluation of the above-mentioned criteria. Within the framework of these benefits and limitations, it is our opinion that self-administration of biologics is a potential pillar for the management of asthma and CSU, and will become increasingly common in the future. In this light, the current pandemic warrants comment, since with lockdowns and travel restrictions, and with more individuals spending more time in home environments, and with restricted access to health-care facilities, self-administration has the potential to allow for continuous administration of the biologic drug on an autonomous basis, with the confidence that they are still receiving full support from their prescriber.

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