Omalizumab and other biologics in drug desensitization

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Purpose of review
Omalizumab has been proposed for controlling adverse reactions during drug desensitization. Our aim is to know the current evidence involving the use of omalizumab in drug-allergy desensitization.

Recent findings
Drug-allergy desensitization is not risk free, but it is a useful procedure and has been applied for drug hypersensitivity reactions with mast cells degranulation through IgE and non-IgE mechanisms. Since 2007, omalizumab has been considered as a potential strategy to prevent adverse reactions.
Our review found few case reports and only one randomized double-blind, placebo-controlled study, using different omalizumab regimens prior to drug desensitization. This scarce evidence is insufficient to predict the effectiveness of omalizumab in rapid drug desensitization procedures, but it may be useful in future studies of omalizumab or related next-generation antibodies.

Summary
Omalizumab or other IgE-targeting biologics, either a fixed dose of 300 mg omalizumab or a dose-related total IgE level and body mass weight may be an option for patients with IgE-mediated or mast cell drug reactions in troublesome desensitization.

Keywords
drug-allergy desensitization, drug reactions, omalizumab

INTRODUCTION

Mechanisms involved in drug hypersensitivity

Drug hypersensitivity reaction (DHR) usually refers to the specific immune response to a drug through antigen-dependent stimulation, such as a hapten-carrier complex. As Pichler points out [1▪], it can also occur through direct binding to receptors on immune or inflammatory cells and subsequent stimulation. Direct drug interactions with immune receptors, such as human leukocyte antigens (HLA) or T-cell receptors (TCR), or with enzymes or receptors of inflammatory cells can also drive DHR.

Studying the timing of DHR onset is a very useful approach for distinguishing immediate reactions with mast cell degranulation from the IgG and common T-cell reactions, although it is not always easy to obtain these data. The immediate appearance of urticaria or anaphylaxis is considered an indicator of IgE and mast cell degranulation, except in NSAIDs hypersensitivity where symptoms may develop 6–24 h after NSAID intake [2], whereas the delayed appearance of severe cutaneous or organ-specific reactions depends on activation of T cells [3].

The mode of drug action has also been proposed as basis for classifying DHRs [4], as it may explain differences in sensitization, dose dependence, HLA restriction, and cross-reactivity [1▪]. This classification of DHR makes a distinction between allergic/immune, p–i stimulation and pseudo-allergic reactions. The allergic/immune reactions because of antigen formation result in all types of Gells and Coombs-mediated immune reactions; p–i stimulation of HLA and TCR drive T-cell reactions, including cutaneous severe reactions; and pseudo-allergic reactions with heterogeneous phenotype are because of stimulation of inflammatory mechanisms through direct binding to receptors such as

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KEY POINTS

- Rapid drug desensitization is a treatment modality by which mast cells are rendered hyporesponsive, protecting patients against IgE-mediated or mast cell drug reactions (urticaria, anaphylaxis).
- Either a fixed dose of 300 mg of omalizumab or a dose-related total IgE level and body mass weight were used in troublesome drug desensitization from one to two weeks before primary drug treatment.
- A dose-related total IgE level and body mass weight of omalizumab for 16 weeks prior to ASA desensitization has been used in a clinical trial in AERD patients with good outcomes in terms of efficacy and safety.
- Omalizumab and other new IgE-targeting biologics may be an option for patients with IgE-mediated or mast cell drug reactions for troublesome desensitization in spite of premedication.

MRPGPRX2, or enzymes like cyclooxygenase or bradykinin [1▪,2].

Drug-allergy desensitization

Sensitization seems to be accompanied by the transient and selective unresponsiveness of mast cells to the drug given. A normal drug dose will provoke mast cell degranulation through IgE and non-IgE mechanisms [5] and the main associated symptoms of urticaria/anaphylaxis after a short drug-free interval [1▪] of mast cell unresponsiveness. This seems to be a normal process in IgE/mast cell reactions to protein allergens and is probably the basis for so-called desensitization [1▪]. Desensitized mast cells do not release significant amounts of mediators of early and late response, and they are drug-specific [6].

Rapid drug desensitization is a treatment modality by which mast cells are rendered hyporesponsive, protecting patients against anaphylaxis [7]. Moreover, mast cell models have provided evidence of profound inhibitory mechanisms of cell activation during desensitization [8]. The internalization of antigen-specific IgE bound to the α-chain of FceRI decreased after rapid desensitization in mouse mast cells [9], without complete disappearance of surface IgE and FceRI when bound to small doses of antigen or disappearance of Syk, as pointed out by Zhao *et al.* [10].

Penicillin desensitization has been widely used as it was first reported as safe and effective in the mid-20th century. The protocol used – a 10-fold escalation in solution concentration with 20 min intervals – has been used as a model for developing drug desensitization ever since [11,12].

Nowadays, desensitization is achieved by incrementally escalating (usually doubling) the suboptimal doses of the culprit drug until the required dose is reached [13]. An in-vitro model of rapid IgE desensitization indicates that both the time and dose are critical to mast cell degranulation [14,15]. Recently, these protocols have been developed for chemotherapeutic and biological agents, allowing administration of first-line therapies that may be critical for patients' quality of life and life expectancy [12,16,17]. However, protocols for delayed reactions have not yet been standardized or may even be contraindicated under circumstances like severe cutaneous adverse reactions, immune thrombocytopenia, serum sickness-like reactions, and so on. [18]. Through evidence is so sparse that desensitization in delayed reactions is an unresolved question.

Omalizumab

Omalizumab (Xolair; Novartis) is a recombinant DNA-derived humanized IgG1 monoclonal antibody, initially approved in 2003 in the USA for the treatment of severe, poorly controlled allergic asthma in children and adults aged at least six years with an elevated serum-IgE level and evidence by skin testing or specific IgE of perennial allergen sensitization [19]. In 2014, it was approved for the treatment of chronic idiopathic urticaria for patients aged 12 years or more [20].

In asthma, the omalizumab dose (75–375 mg) and dosing frequency (2–4 weeks) by subcutaneous route are determined prior to starting treatment by serum total IgE level (IU/ml) and body weight (kg) [20]. For chronic idiopathic urticaria, there is a fixed range of 150–300 mg subcutaneous route, independent of IgE level or body weight [20].

However, omalizumab has also been studied as an off-label treatment for several allergic conditions, including atopic dermatitis, food allergy, eosinophilic gastrointestinal disease, allergic rhinitis, idiopathic anaphylaxis, systemic mastocytosis, and even allergic bronchopulmonary aspergillus with high IgE titers or adjunct to immunotherapy [21,22].

Omalizumab specifically binds to the C epsilon 3 domain of free IgE at the site of the FceRI receptor and does not cross-link surface-bound IgE, so it should not trigger effector cell degranulation [23]. The complexes formed between omalizumab and IgE result in a significant decrease in free IgE in serum. They also prevent IgE from binding to effector cells, resulting in decreased mediator release in response to allergens [24] and a reversible down-regulation of FceRI receptors on basophils, mast cells, and dendritic cells [25,26].

METHODS AND RESULTS

Omalizumab in desensitization of IgE-mediated, NSAID, and other types of drug reactions

We conducted a review of articles published from 2003 to 2020 and involving the use of omalizumab with drug-allergy desensitization. PubMed, Embase, Scopus, and the Web of Knowledge were searched using the terms of 'omalizumab' and 'drug desensitization.' Results are shown in Table 1 [27–32,33▪, 34–38].

The search yielded a few case reports where omalizumab was successfully used prior to drug desensitization: in one case to insulin [29]; in another, to the enzyme Elosulfase α [35]; and in three cases to chemotherapeutics agents – two to carboplatin [37,38] and one to oxaliplatin [36]. But there was only one clinical assay ($n = 11$) in aspirin-exacerbated respiratory disease (AERD) where omalizumab was used previous to acetylsalicylic acid (ASA) desensitization for 16 weeks in a double-blind, placebo-controlled, randomized trial [32]. In most of the reported cases, omalizumab was used in a fixed dose of 300 mg, but the duration of pretreatment ranged from 7 to 15 days [29,36–38]. In the other two, omalizumab dose was related to total IgE levels and body mass weight [31,35]. In one study, the drug was administered just four days before the desensitization [35], and in all but one (in desensitization to carboplatin [37]) patients continued to receive omalizumab after desensitization.

In the AERD clinical assay [32], the omalizumab dose was adjusted to total IgE level and body mass weight along 16 weeks of pretreatment, but it was stopped it after desensitization was achieved [32]. All 11 participants had moderate to severe persistent asthma and were receiving combination controller therapy (montelukast and inhaled corticosteroids and in all but one patient, long-acting β agonists). Compared with controls, there was an overall difference in urinary leukotriene E4 (LTE4) levels in participants who received omalizumab and did not have a respiratory reaction during desensitization; however, this difference was significant only after the 100-mg ASA dose [32]. Although this was a small study, the difference in respiratory response patterns during aspirin desensitization was statistically significant, but the findings cannot be generalized to any AERD patients who have not received omalizumab for 16 weeks previous to ASA desensitization as the authors suggested [32].

Table 1. Omalizumab in drug desensitization

Year	Type of reaction	Drug	Desensitization drug	Number of patients	Cotreatment	Omalizumab schedule	Omalizumab after desensitization	Reference	Journal
2009	IgE-mediated urticaria	Insulin	No	1	No	IgE related	Yes	[27]	*NEJM*
2018	Anaphylaxis	Insulin	No	1	No	150 mg/4 weeks	Yes	[28]	*Diabetic Medicine*
2007	Anaphylaxis	Insulin	Yes	1	No	300 mg/15 days	Yes	[29]	*JACI*
2015	AERD		No	1	Asthma treatment	IgE related	Yes	[30]	*JACI in Practice*
2015	AERD		Yes/Aspirin	1	Asthma treatment	IgE related	Yes	[31]	*JIACI*
2018	AERD		Yes/Aspirin	11	Asthma treatment	IgE related/ 16 weeks	No	[32]	*Annal A C Inmunol*
2018	AERD		Yes/Aspirin	167	Asthma treatment	No	No	[33▪]	*JACI*
2017	IgE mediated urticaria	Elosulfase α	Yes	1	No	No	No	[34]	*JACI in Practice*
2019	Anaphylaxis	Elosulfase α	Yes	1	No	IgE related/4 days	Yes	[35]	*PAI*
2019	Anaphylaxis	Oxaliplatin	Yes	1	No	300 mg/7 days	Yes	[36]	*JIACI*
2014	Anaphylaxis	Carboplatin	Yes/ Carboplatin	1	No	300 mg/9 days	No	[37]	*JACI in Practice*
2020	Anaphylaxis	Carboplatin	Yes	1	No	300 mg/15 days	Yes	[38]	*Clinical Translational Allergy*

Case reports and studies where omalizumab was used as pretreatment before desensitization and other cases where it was used to treat the drug reactions without desensitization [27–32,33▪,34–37]. AERD, aspirin-exacerbated respiratory disease.

Unresolved questions about the use of omalizumab in drug desensitization

The available evidence is insufficient to thoroughly answer the questions posed by Casale *et al.* [39] in response to the first case reported in 2007.

What is the optimal duration of pretreatment with omalizumab for desensitization to a drug provoking an allergic reaction? [39]

Studies have used either a fixed dose of 300 mg or a dose adjusted to total IgE level and body mass weight; the minimum duration of pretreatment tested has been 1–2 weeks prior to desensitization, although in the AERD study pretreatment lasted for 16 weeks.

Can you stop the omalizumab and still tolerate the drug with or without desensitization? [39]

Available evidence suggests that the answer is no. In one case study, carboplatin was discontinued concurrently with omalizumab, whereas all others reported continuing treatment with omalizumab. Only in the AERD study did patients stop receiving the drug after 16 weeks of pretreatment and successful desensitization to ASA. However, in the case reported by Guillen *et al.* [31], successful desensitization to ASA was achieved in a patient with AERD, but they followed with omalizumab 150 mg/month. In this case, there was an association between AERD and chronic urticaria, which returned in the two attempts to withdraw omalizumab, though the respiratory symptoms did not.

What immunologic and clinical endpoints of interest could help predict the ability to use omalizumab in this fashion and to possibly stop the omalizumab after reaching maintenance therapy? [39]

For now, this question has barely been addressed. However, determinations of mediators such as tryptase, skin tests, or in-vitro tests that elucidate the participation of IgE in a drug reaction might indicate the use of omalizumab in any troublesome desensitization. This is even the case where only clinical data would suggest mast cell degranulation.

Future challenge

Recently, a next-generation high-affinity anti-IgE monoclonal antibody, QGE031 (ligelizumab), has been developed, which binds the Cε3 domain of IgE with higher affinity (50-fold-higher *in vitro* and six to nine-fold greater potency *in vivo*) than omalizumab and is currently in phase III clinical trials. Ligelizumab was found to have a larger suppressive effect than omalizumab on circulating IgE, basophil FcεRI expression, and skin prick test responses to allergens [40]. Several controlled trials in allergic asthma and chronic urticaria have demonstrated that ligelizumab has greater efficacy than omalizumab against inhaled and skin allergy responses [41]. Gasser *et al.* [42] have also described the crystal structure of ligelizumab bound to IgE and the epitope differences between ligelizumab and omalizumab that contribute to their qualitatively distinct IgE-receptor inhibition profiles.

MEMP1972A (quilizumab) is another humanized, monoclonal IgG1 that binds to the M1-prime segment present on membrane-expressed IgE, but not on soluble IgE in serum [42]. This drug has already been evaluated in phase I and II clinical trials, showing good safety, tolerability, and anti-CmX activity [43,44]. Quilizumab was also recently assessed in adults with allergic asthma that was poorly controlled despite high-dose inhaled corticoid steroids and a second controller [43]. After 36 weeks of treatment, quilizumab was well tolerated, with a safety profile consistent with previous clinical studies; however, it did not have a clinically significant impact on exacerbation rates, lung function, or quality of life [45].

Finally, MEDI4212, another IgE-targeting biologic, binds not only to soluble but also to membrane IgE. It may achieve an immediate clinical benefit by directly targeting free IgE, while limiting the generation of new IgE-switched B cells and plasma cells [46]. In one phase I study, MEDI4212 treatment decreased serum IgE more rapidly than omalizumab treatment, but IgE recovery was also much more rapid than in the omalizumab-treated group [47]. This feature might limit the potential for dosing-schedule advantages over omalizumab, but it may be used as pretreatment in drug desensitization protocols where prolonged use of this biological agent is not necessary.

All of these next-generation high-affinity anti-IgE monoclonal antibodies can be potential drugs to be particularly considered in troublesome desensitization of IgE mediated drug reactions.

CONCLUSION

Omalizumab and other new IgE-targeting biologics may be an option for patients with IgE-mediated or mast cell drug reactions for troublesome desensitization in spite of premedication. Discontinuation of omalizumab is safe only for ASA desensitization in AERD patients. In other cases, the discontinuation of omalizumab may condition symptoms' reappearance.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Pichler WJ. Immune pathomechanism and classification of drug hypersensi-
■ tivity. Allergy 2019; 74:1457–1471.

Excellent update on the classification of drug hypersensitivity.

2. Blanca-Lopez N, Somoza-Alvarez ML, Bellon T, *et al.* NSAIDs hypersensitivity: questions not resolved. Curr Opin Allergy Clin Immunol 2018; 18:291–301.
3. Pichler WJ, Hausmann O. Classification of drug hypersensitivity into allergic, p-i, and pseudo-allergic forms. Int Arch Allergy Immunol 2016; 171:166–179.
4. Pichler WJ, Adam J, Watkins S, *et al.* Drug hypersensitivity: how drugs stimulate T cells via pharmacological interaction with immune receptors. Int Arch Allergy Immunol 2015; 168:13–24.
5. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006; 26:451–463.
6. Sancho-Serra M, Simarro M, Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FceRI internalization. Eur J Immunol 2011; 41:1004–1013.
7. Mezzano V, Giavina-Bianchi P, Picard M, *et al.* Drug desensitization in the management of hypersensitivity reactions to monoclonal antibodies and chemotherapy. BioDrugs 2014; 28:133–144.
8. Castells Guitart MC. Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. J Investig Allergol Clin Immunol 2014; 24:72–79.
9. Oka T, Rios EJ, Tsai M, *et al.* Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. J Allergy Clin Immunol 2013; 132:922–932.
10. Zhao W, Gomez G, Macey M, *et al.* In vitro desensitization of human skin mast cells. J Clin Immunol 2012; 32:150–160.
11. Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to B-lactam antibiotics. J Allergy Clin Immunol 1987; 80:314–319.
12. Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol 2006; 6:476–481.
13. Sloane D, Govindarajulu U, Harrow-Mortelliti J, *et al.* Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. J Allergy Clin Immunol Pract 2016; 4:497–504.
14. Morales AR, Shah N, Castells M. Antigen-IgE desensitization in signal transducer and activator of transcription 6-deficient mast cells by suboptimal doses of antigen. Ann Allergy Asthma Immunol 2005; 94:575–580.
15. de las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MA. Drug hypersensitivity and desensitizations: mechanisms and new approaches. Int J Mol Sci 2017; 18:1316.
16. Brennan PJ, Bouza TR, Hsu FI, *et al.* Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 2009; 124:1259–1266.
17. Bonamichi-Santos R, Castells M. Diagnoses and management of drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: reactions to taxanes and monoclonal antibodies. Clin Rev Allergy Immunol 2018; 54:375–385.
18. Macy E, Romano A, Khan D. Practical management of antibiotic hypersensitivity in 2017. J Allergy Clin Immunol Pract 2016; 5:577–586.
19. Normansell R, Walker S, Milan SJ, *et al.* Omalizumab for chronic asthma in adults and children. Cochrane Database Syst Rev 2014; CD003559.
20. Xolair Full Prescribing Information. Genentech. Revised 5/2019. https://www.gene.com/download/pdf/xolair_prescribing.pdf (accessed December, 2019).
21. Babu KS, Polosa R, Morjaria JB. Anti-IgE-emerging opportunities for omalizumab. Expert Opin Biol Ther 2013; 13:765–777.
22. Incorvaia C, Mauro M, Makri E, *et al.* Two decades with omalizumab: what we still have to learn. Biologics 2018; 12:135–142.
23. Easthope S, Jarvis B. Omalizumab. Drugs 2001; 61:253–260.
24. MacGlashan D. Loss of receptors and IgE in vivo during treatment with anti-IgE antibody. J Allergy Clin Immunol 2004; 114:1472–1474.
25. Saini SS, MacGlashan DW Jr, Sterbinsky SA, *et al.* Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. J Immunol 1999; 162:5624–5630.
26. Beck LA, Marcotte GV, MacGlashan D, *et al.* Omalizumab-induced reductions in mast cell FcεRI expression and function. J Allergy Clin Immunol 2004; 114:527–530.
27. Yong PF, Malik R, Arif S, *et al.* Rituximab and omalizumab in severe, refractory insulin allergy. N Engl J Med 2009; 360:1045–1047.
28. Mishra S, Connors L, Tugwell B. Role of omalizumab in insulin hypersensitivity: a case report and review of the literature. Diabet Med 2018; 35:663–666.
29. Matheu V, Franco A, Pérez E, *et al.* Omalizumab for drug allergy. J Allergy Clin Immunol 2007; 120:1471–1472.
30. Bergmann KC, Zuberbier T, Church MK. Omalizumab in the treatment of aspirin-exacerbated respiratory disease. J Allergy Clin Immnunol Pract 2015; 3:459–460.
31. Guillen D, Bobolea I, Calderon O, *et al.* Aspirin desensitization achieved after omalizumab treatment in a patient with aspirin exacerbated urticaria and respiratory disease. J Invest Allergol Clin Immunol 2015; 25:133.
32. Lang DM, Aronica MA, Maierson ES, *et al.* Omalizumab can inhibit respiratory reaction during aspirin desensitization. Ann Allergy Asthma Immunol 2018; 121:98–104.
33. Waldram J, Walters K, Simon R, *et al.* Safety and outcomes of aspirin
■ desensitization for aspirin exacerbated respiratory disease: a single center study. J Allergy Clin Immunol 2018; 141:250–256.

Only clinical trial where omalizumab is used in desensitization to ASA in AERD.

34. Guvenir H, Dibek Misirlioglu E, Capanoglu M, *et al.* Successful desensitization of elosulfase alfa-induced anaphylaxis in a pediatric patient with Morquio syndrome. J Allergy Clin Immunol Pract 2017; 5:1156–1157.
35. Arroabarren E, Aznal E, Anda M, Sanchez-Valverde F. Anaphylaxis after elosulfase A infusion: omalizumab as coadyuvant for enzyme replacement therapy desensitization. Pediatr Allergy Immunol 2019; 31:491–494.
36. Prieto-Garcia A, Noguerado B, Rojas P, *et al.* Unexpected anaphylaxis after completing a desensitization protocol to oxaliplatin: successful adjuvant use of omalizumab. J Investig Allergol Clin Immunol 2019; 29:53–55.
37. Ojaimi S, Harnett PR, Fulcher DA. Successful carboplatin desensitization by using omalizumab and paradoxical diminution of total IgE levels. J Allergy Clin Immunol Pract 2014; 2:105–106.
38. Oude Elberink H, Jalving M, Hilda Dijkstra H, van de Ven A. Modified protocol of omalizumab treatment to prevent carboplatin-induced drug hypersensitivity reactions: a case study. Clin Transl Allergy 2020; 10:5.
39. Casale TB. Replay to 'Omalizumab for drug allergy. J Allergy Clin Immunol. 2007'. J Allergy Clin Immunol 2007; 120:1472–1473.
40. Arm JP, Bottoli I, Skerjanec A, *et al.* Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy 2014; 44:1371–1385.
41. Maurer M, Gimenez-Arnau AM, Sussman G, *et al.* Ligelizumab for chronic spontaneous urticaria. N Engl J Med 2019; 381:1321–1332.
42. Gasser P, Tarchevskaya SS, Guntern P, *et al.* The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat Commun 2020; 11:165.
43. Gauvreau GM, Arm JP, Boulet LP, *et al.* Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J Allergy Clin Immunol 2016; 138:1051–1059.
44. Harris JM, Maciuca R, Bradley S, *et al.* Efficacy and safety of quilizumab in adults with allergic asthma inadequately controlled on inhaled corticosteroids and a second controller (COSTA Study). Am J Respir Crit Care Med 2015; 191:A5168.
45. Harris JM, Maciuca R, Bradley MS, *et al.* A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. Respir Res 2016; 17:29.
46. Nyborg AC, Zacco A, Ettinger R, *et al.* Development of an antibody that neutralizes soluble IgE and eliminates IgE expressing B cells. Cell Mol Immunol 2016; 13:391–400.
47. Sheldon E, Schwickart M, Li J, *et al.* Pharmacokinetics, pharmacodynamics, and safety of MEDI4212, an anti-IgE monoclonal antibody, in subjects with atopy: a phase I study. Adv Ther 2016; 33:225–251.