

Plasmapheresis Prior to Omalizumab Administration in a 15-Year-Old Boy with Severe Asthma and Very High IgE Levels: Sustained Effect Over 2 Years

Plasmapherese vor Omalizumab-Gabe ermöglicht eine Anti-IgE-Therapie trotz sehr hoher IgE-Serumspiegel bei einem 15-jährigen Jungen

Authors

S. Kerzel¹, M. Zemlin¹, T. Rogosch¹, M. Ollert², H. Renz³, G. Klaus¹, R. F. Maier¹

Affiliations

¹ Department of Pediatrics, Philipps-University, Marburg, Germany

² Clinical Research Division of Molecular and Clinical Allergotoxicology, Department of Dermatology and Allergy, Technical University Muenchen, Germany

³ Department of Clinical Chemistry and Molecular Diagnostics, Philipps-University, Marburg, Germany

Key words

- asthma
- IgE
- omalizumab
- plasmapheresis

Schlüsselwörter

- Asthma
- IgE
- Omalizumab
- Plasmapherese

Abstract

Background: Anti-IgE therapy with omalizumab is an innovative therapy option in patients with severe allergic asthma. However, many patients are excluded from this treatment due to very high serum IgE levels which lie above the weight-dependent cut-off for a reasonable omalizumab administration (700 kU/l).

Objective: We sought to evaluate whether a preceding plasma exchange is suitable to establish the starting basis for a subsequent anti-IgE therapy in a 15 year-old boy with steroid-resistant unstable allergic asthma whose pretreatment serum IgE levels ranged between 3000 and 8000 kU/l.

Methods: Our aim was to create a period with relatively low IgE serum concentrations, which could be overridden by a high dose of omalizumab. 3 sessions of plasmapheresis were performed and 3 × 3000 ml plasma were exchanged against albumin solution.

Results: We removed an absolute amount of 8650 kU total IgE. During plasmapheresis, serum IgE levels markedly declined and fell below 500 kU/l. Immediately after the third plasma exchange, we started omalizumab therapy. As expected, total IgE levels began to rise again upon cessation of plasmapheresis, and after 2 months the pre-treatment values were reached. In contrast, serum concentrations of free IgE remained stable on a level of about 80 kU/l during the whole observation period. During this period, the boy displayed a considerable improvement of asthma control and an increase in quality of life. In addition, his previously poor lung function normalized.

Conclusions: Plasmapheresis prior to omalizumab administration is suitable to temporarily reduce grossly elevated serum IgE levels and might facilitate anti-IgE therapy in selected patients previously considered not suitable for this therapy.

Zusammenfassung

Hintergrund: Die Gabe von Anti-IgE-Antikörpern (Omalizumab) ist eine innovative Therapieoption bei Patienten mit schwerem allergischem Asthma. Vielen Patienten bleibt diese Therapie jedoch verwehrt, da sie sehr hohe IgE-Spiegel haben, welche über dem oberen Grenzwert für eine Omalizumab-Therapie liegen.

Fragestellung und Methoden: Die Fragestellung unseres Heilversuchs war daher, ob durch eine vorausgehende Plasmapherese der IgE-Serumspiegel bei einem 15-jährigen Jungen mit schwerem steroidresistentem Asthma und mit sehr hohen IgE-Spiegeln (bis 8000 kU/l) derart gesenkt werden kann, dass eine erfolgversprechende Ausgangsbasis für eine Anti-IgE-Therapie geschaffen wird.

Ergebnisse: Im Rahmen von 3 Plasmapheresen tauschten wir insgesamt 9000 ml Plasma aus und entfernten dabei 8650 kU IgE (absolut). Hierdurch sanken die IgE-Spiegel stark ab und fielen auf Werte unter 500 kU/l. In dieser Phase der niedrigsten IgE-Spiegel begannen wir eine Omalizumab-Therapie. Während die Serumspiegel an Gesamt-IgE erwartungsgemäß wieder stiegen, blieben die Spiegel an freiem IgE (= nicht an Omalizumab komplexiert) während der gesamten Beobachtungsperiode auf einem bemerkenswert niedrigen Niveau von 80 kU/l. Parallel zu den laborchemischen Veränderungen zeigte sich eine deutliche klinische Besserung der Asthmasymptomatik.

Schlussfolgerungen: Die Plasmapherese vor Omalizumab-Therapie ist somit geeignet, IgE-Serumspiegel signifikant zu reduzieren. Sie könnte ein zusätzlicher Therapiebaustein bei ausgewählten Patienten sein, bei denen sehr hohe IgE-Spiegel einer Erfolg versprechenden Anti-IgE-Therapie im Wege stehen.

Bibliography

DOI <http://dx.doi.org/10.1055/s-0031-1287824>
Published online:
October 19, 2011
Klin Padiatr 2011; 223: 356–359
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0300-8630

Correspondence

Dr. Sebastian Kerzel
Department of Pediatrics
Philipps-University
Baldingerstraße
D-35033 Marburg
Germany
Tel.: +49/6421/5862 650
Fax: +49/6421/5863 619
kerzel@med.uni-marburg.de

Non-standard abbreviations

▼	
DPI	dry powder inhaler
FeNO	fractional exhaled nitric oxide
FEV	forced expiratory volume
GINA	Global Initiative Against Asthma
MEF	mid-expiratory flow
MDI	metered dose inhaler
PBMC	peripheral blood mononuclear cell
PEF	peak expiratory flow
PICU	pediatric intensive care unit
_s R	specific airway resistance

Introduction

Immunoglobulin E (IgE) plays an important role in the pathogenesis of allergic asthma [5, 15]. Bound to mast cells in the airway mucosa, IgE generates the interface between the allergen and the immune system and hence critically participates in the mediation of the local inflammatory response [11]. It has long been questioned whether the removal of humoral inflammatory factors by means of plasma exchange could improve the clinical condition in asthma [8]. However, reports about the use and the effectiveness of plasmapheresis in severe asthma are very rare and the outcomes of the patients were not encouraging with regard to long-term disease control [2, 8, 9, 17]. All these studies examined the effect of an isolated plasma exchange in severe asthma without an additional simultaneous immunomodulating approach. Our aim was to evaluate whether a preceding plasma exchange is suitable to establish the starting basis for a subsequent anti-IgE therapy in an asthma patient with very high IgE serum levels.

Omalizumab is a humanized monoclonal anti-IgE antibody [6, 20], which was licensed for the application in patients with serum IgE level below 700 kU/l when the patient presented [13] and below 1500 kU/l since 2010, which precludes many patients with severe allergic asthma who have IgE levels above this cut-off.

Case report

We report our observations on the application of a plasma exchange procedure preceding anti-IgE therapy in a 15-year-old boy with severe allergic asthma whose serum IgE levels varied between 3000 and 8000 kU/l [16]. During childhood, the boy had dozens of hospital admissions due to acute exacerbations. In the year before the first admission to our department, he had 4 emergency admissions, including 2 admissions to the PICU. On presentation in our outpatient clinic for Pediatric Allergology and Pneumology, he suffered from constant dry cough, dyspnea and wheezing. He reported repeated awakening every night due to asthma symptoms. The physical capacity was reduced with a limitation in daily activities. As the supervisory school authority had declined the further school attendance, the boy was at home since more than 1 year. Lung function at that time was heavily impaired with a severe bronchial obstruction (FEV₁: 49%, MEF₅₀: 30%, MEF₂₅: 22%, _sR: 278%) and an accompanying pseudo-restriction. FeNO was 114 ppb (Niox mino®; Aerocrine, Solna, Sweden). According to GINA criteria [10], this asthma has to be classified as severe asthma. Skin prick test revealed a significant

sensitization against grass pollen, rye pollen, *Cladosporium herbarum*, cat dander, dog dander, horse hair, and rabbit hair. Serologic laboratory tests at initial presentation in our department showed a highly elevated specific IgE against *Phleum pratense*, rye, dog, and cat with a total IgE of 4170 kU/l (● Table 1). When we took over medical care, the boy had an extensive anti-asthmatic therapy, including oral steroids, which had induced an iatrogenic Cushing syndrome. The detailed characteristics of the pharmacotherapy on initial presentation are shown in ● Table 2. Although formally the boy was a good candidate for a therapeutic attempt with omalizumab, the high serum IgE level precluded an application according to the current guidelines. Therefore, we sought a way to reduce the boy's pre-treatment IgE load. The general idea was to create a period with relatively low IgE serum concentrations, which could be overridden by a stoichiometrically high dose of omalizumab.

After informed consent, plasmapheresis was performed with a BM25 blood monitor and balance system (Edwards Lifesciences, Unterschleißheim, Germany) using a BT900 membrane plasmafilter. During each of 3 plasmapheresis sessions, a total of 3000 ml was exchanged against a 5% albumin solution. Overall, we removed an absolute amount of 8650 kU IgE (measured in plasmapheresis filtrate). The dynamics of total serum IgE levels are shown in ● Fig. 1. Our aim was to push the IgE level below the margin of 700 kU/l (upper cut off for omalizumab therapy), which was achieved during the third plasma exchange. The lowest serum IgE value we observed was 483 kU/l after the last plasmapheresis. Immediately after the third plasmapheresis session, we began an omalizumab therapy with 450 mg omalizumab (Xolair®) s.c. every 2 weeks.

Upon cessation of plasmapheresis, total serum IgE levels began to rise despite the anti-IgE therapy (● Fig. 2). After 2 months, pre-treatment values were reached again. This development was expected, as the used commercial IgE assay cannot distinguish between free IgE and complexed IgE [12]. The total IgE concentration is the sum of free IgE molecules and IgE-containing immune complexes with omalizumab [18]. As these IgE-omalizu-

Table 1 Relevant laboratory findings before plasmapheresis.

	Actual value	Reference range
total IgE	4170 kU/l	[< 100 kU/l]
specific IgE against		
<i>phleum pratense</i>	35 kU/l	[< 0.35 kU/l]
rye pollen	25 kU/l	[< 0.35 kU/l]
cat	209 kU/l	[< 0.35 kU/l]
dog	186 kU/l	[< 0.35 kU/l]
leukocytes	11.4 G/l	[4.5–10 G/l]
eosinophils	22 %	[1–4 %]

Table 2 Pharmacotherapy on first presentation in our outpatient clinic.

Agent	Daily dose
fluticasone/salmeterol	500 µg/50 µg bid per DPI (Diskus®)
formoterol	12 µg per pMDI
prednisolone	50 mg p. o.
omeprazole	20 mg p. o.
montelukast	10 mg p. o.
ipratropiumbromide/fenoterol	20 µg/50 µg p. r. n per pMDI (was actually used 10–12 times a day)
cetirizine	10 mg p. o.
NaCl 0.9 %	2 ml tid per nebulizer

DPI: dry powder inhaler; pMDI: pressurized metered dose inhaler

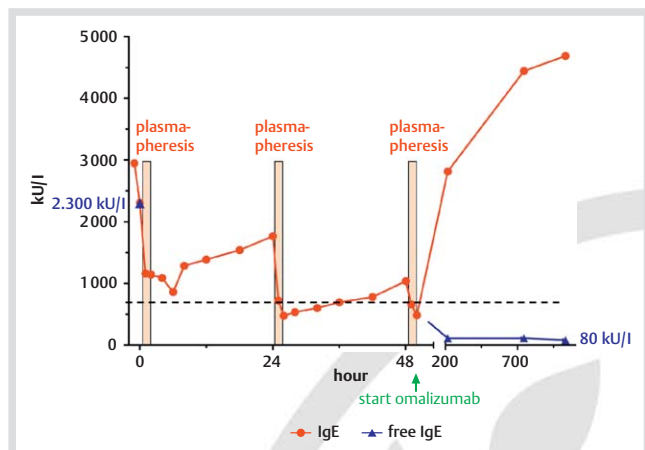


Fig. 1 Kinetics of serum IgE during and after plasma exchange. The IgE level fell sharply during each plasmapheresis session and rose again afterwards. The lowest IgE value was observed directly after the third plasma exchange. In this trough, anti-IgE therapy was initiated. While total IgE levels steadily increased within the next days, levels of free IgE remained low.

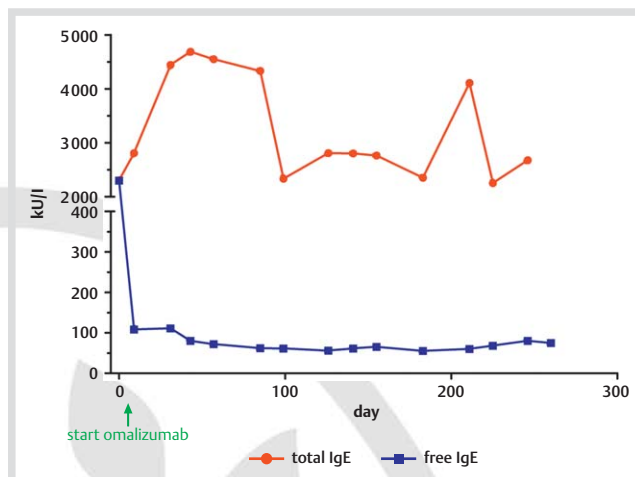


Fig. 2 Kinetics of total and free IgE during 10 months of omalizumab therapy. Despite the anti-IgE therapy, levels of total IgE began to climb again after cessation of plasmapheresis. The pre-treatment values were reached after 2 months of therapy. In contrast, the free IgE levels remained permanently low on a level below 100 kU/l.

mab complexes remain in the circulation until degradation in the liver, they contribute to the measured “total IgE” value [7]. Therefore, in addition to the commercial standard IgE assay, we also determined the free IgE levels [3]. In contrast to total IgE, the free IgE remained stable on a remarkably low level of about 80 kU/l during anti-IgE therapy (○ Fig. 2).

The anti-IgE treatment was accompanied by a noticeable clinical improvement. Due to subjective assessment (Asthma control test), the frequency of dyspnea and the severity of cough attacks markedly declined. His lung function improved and 1 month after therapy start, the FEV₁ increased and the specific resistance began to fall (○ Fig. 3). 10 months after therapy onset, he displayed a normal lung function analysis without obstruction (FEV₁: 103%, MEF₅₀: 118%, MEF₂₅: 102%, sR: 162%). The general clinical amelioration was accompanied by a drop in fractional exhaled nitric oxide (FeNO) which went down from 114 ppb to 17 ppb (normal range: <30 ppb) after 10 months. 1 year after onset of the anti-IgE therapy, the boy's asthma had stabilized and he re-entered school. He had no further hospital admissions since the onset of this therapy. The last follow-up in our department was 2 years after the intervention and the begin of omalizumab therapy. At that time, the boy was well and the asthma still controlled. By now, he attends a special residential school for asthmatic children.

Discussion

There has been 1 small randomized pilot study in which Ellingsen and co-workers examined the effect of plasmapheresis on asthma symptoms, PEF, need for systemic steroids, and requirement for beta-agonists in 4 adult asthma patients [8]. After removing humoral factors over a 10 day period, none of the 4 patients displayed a significantly amelioration of the clinical condition. Therefore, the authors concluded that plasmapheresis is no treatment option in this patient group [8]. However, considering the IgE kinetics in our study with a doubling of serum levels within 24 h, it is not surprising that a temporally limited removal of inflammatory factors over a period of some days has no

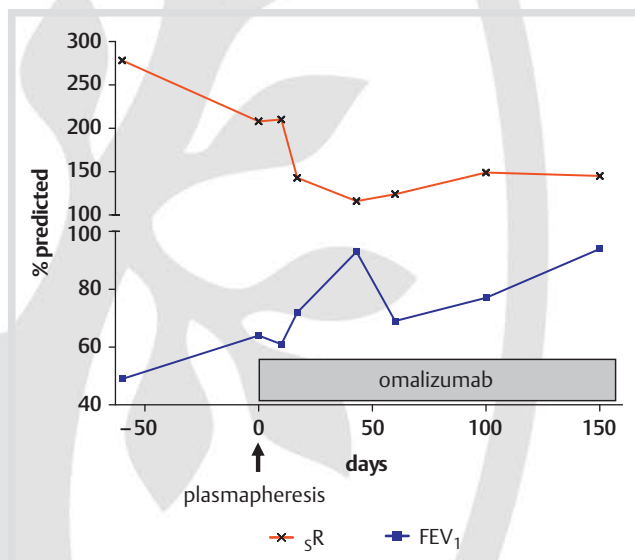


Fig. 3 Lung function before and after plasmapheresis. After plasma exchange and during omalizumab therapy the lung function continuously improved. The FEV₁ clearly grew while the specific resistance (sR) decreased. During this period, anti-asthmatic therapy with steroids was not altered.

long-lasting benefit on disease activity. Our results show that the initial IgE levels are restored within days after cessation of plasmapheresis. This finding is in line with Lassalle et al., who described a patient with aspirine-sensitive asthma and IgE antibodies against platelets [17]. Plasma removal by plasmapheresis in this patient induced a clinical improvement in parallel to a decrease in circulating anti-platelets IgE antibodies. After withdrawal of therapy however, all respiratory symptoms reappeared progressively within 2 weeks.

Therefore, in our present study we did not merely seek to remove as much IgE as possible, because we anticipated the withdrawn IgE to be replaced very rapidly after cessation of plasmapheresis. Instead, our approach was to create a period with relatively low IgE serum concentrations, which could be overrid-

den by a stoichiometrically high dose of omalizumab. This phase of low IgE levels could provide the opportunity for anti-IgE antibodies to reach the periphery (e.g. the bronchial mucosa in the lung) and hence exert anti-inflammatory as well as immunomodulating effects. With regard to the favorable clinical course, we consider that the concept in our patient was successful. The boy in our study displayed a marked improvement of asthma control and a noticeable increase in quality of life during the therapy. We consider that this beneficial long-term course was mainly due to the omalizumab treatment following the plasma exchange, which has created the starting-point for an effective anti-IgE therapy. Plasmapheresis has also been used in various non-allergic chronic inflammatory diseases to create a similar temporary "window of opportunity" for promising anti-inflammatory therapies [1,4,19].

Although the course in our patient was encouraging, the potential drawbacks and risks of plasmapheresis are not negligible. The placement of the central catheter is an invasive procedure which bears the risk of bleeding, thrombosis, and infection. Moreover, the costs of plasma exchange are considerable. Therefore, despite the favorable outcome in the present case, we would like to point out that we consider plasma exchange only an additional therapeutic option in very selected patients. However, prior to additional plasma exchange, we would today strongly recommend to discuss the possibility of an isolated off-label administration of a high dose of omalizumab despite high serum IgE levels. Although the current guidelines discourage the use of omalizumab in such a context [14], there are recent reports on the successful use of omalizumab in asthma patients with IgE levels above the licensed cut-offs [21]. Controlled studies with a higher number of patients are needed to evaluate the effectiveness and safety of omalizumab in patients with very high IgE levels.

In conclusion, plasmapheresis might be considered as a valuable additive therapy option in combination with omalizumab in selected patients with severe uncontrolled asthma with very high serum IgE levels after an ineffective treatment attempt with omalizumab alone.

Acknowledgements

▼
We gratefully thank Regina Stoeher, Sabine Jennemann, and Beate Heuser for technical assistance, the team of the PICU Kinderintensivstation 7 and the team of the KfH-Kinderdialyse for the committed support. This work was funded by SFB/TR22 (TP A17) of the Deutsche Forschungsgemeinschaft and by a research grant by the University Hospital Giessen and Marburg GmbH.

Conflict of interest: The authors have no conflict of interest to disclose.

References

- 1 Bambauer R, Jesberger HJ, Limbach HG et al. Single-needle diafiltration and single-needle plasmapheresis in premature infants. *Klin Padiatr* 1986; 198: 408–413
- 2 Bambauer R, Jutzler GA, Micka K et al. Drug-resistant bronchial asthma successfully treated with plasma exchange. *J Clin Apher* 1984; 2: 200–205
- 3 Braren I, Greunke K, Grunwald T et al. Chimeras of human IgE receptor alpha-chain and avian constant immunoglobulin domains for the determination of serum IgE. *Allergy* 2009; 64 (Suppl 90): 81–82
- 4 Brix C, Herberhold T, Bauer A et al. Erfolgreiche Neuromyelitis optica – Behandlung mit Immunadsorption in einem Kind. *Klin Padiatr* 2011; 223 (Suppl 1): S49. doi: 10.1055/s-0031-1273850
- 5 Burrows B, Martinez FD, Halonen M et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989; 320: 271–277
- 6 Busse W, Corren J, Lanier BQ et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108: 184–190
- 7 Casale TB, Bernstein IL, Busse WW et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997; 100: 110–121
- 8 Ellingsen I, Florvaag E, Andreassen AH et al. Plasmapheresis in the treatment of steroid-dependent bronchial asthma. *Allergy* 2001; 56: 1202–1205
- 9 Gartmann J, Grob P, Frey M. Plasmapheresis in severe asthma. *Lancet* 1978; 2: 40
- 10 GINA. Global Initiative for Asthma: Global strategy for asthma management and prevention (2008). <http://www.ginasthma.com>
- 11 Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8: 205–217
- 12 Hamilton RG, Marcotte GV, Saini SS. Immunological methods for quantifying free and total serum IgE levels in allergy patients receiving omalizumab (Xolair) therapy. *J Immunol Methods* 2005; 303: 81–91
- 13 Hochhaus G, Brookman L, Fox H et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003; 19: 491–498
- 14 Holgate S, Buhl R, Bousquet J et al. The use of omalizumab in the treatment of severe allergic asthma: A clinical experience update. *Respir Med* 2009; 103: 1098–1113
- 15 Holgate S, Casale T, Wenzel S et al. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005; 115: 459–465
- 16 Kerzel S, Zemlin M, Rogosch T et al. Plasmapherese ermöglicht eine Omalizumab-Therapie bei einem jugendlichen Asthma Patienten mit sehr hohen IgE-Serumspiegeln. *Klin Padiatr* 2010; 222: 107. doi: 10.1055/s-0030-1251056
- 17 Lassalle P, Joseph M, Ramon P et al. Plasmapheresis in a patient with severe asthma associated with auto-antibodies to platelets. *Clin Exp Allergy* 1990; 20: 707–712
- 18 Lowe PJ, Tannenbaum S, Gautier A et al. Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. *Br J Clin Pharmacol* 2009; 68: 61–76
- 19 Rödl S, Rehak T, Marschitz I et al. 12 Jahre Erfahrung mit extrakorporalen Therapien an einer interdisziplinären pädiatrischen Intensivstation. *Klin Padiatr* 2010; 222 (Suppl 1): S108. doi: 10.1055/s-0030-1261629
- 20 Soler M, Matz J, Townley R et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001; 18: 254–261
- 21 Steiss JO, Strohner P, Zimmer KP et al. Reduction of the total IgE level by omalizumab in children and adolescents. *J Asthma* 2008; 45: 233–236