Respiratory Medicine 155 (2019) 54–57

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Scottish consensus statement on the role of FeNO in adult asthma

Chris RuiWen Kuo[a], Mark Spears[b], John Haughney[c], Andrew Smith[d], Joy Miller[e], Tracey Bradshaw[f], Lorna Murray[g], Peter Williamson[h], Brian Lipworth[a,*]

[a] Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, DD1 9SY, UK
[b] Respiratory Medicine, Forth Valley Royal Hospital, Larbert, FK5 4WR, UK
[c] Clinical R&D, Queen Elizabeth University Hospital, Glasgow, G51 4TF, UK
[d] Department of Respiratory Medicine, University Hospital Wishaw, ML2 0DP, UK
[e] Respiratory Medicine Unit, Aberdeen Royal Infirmary, University of Aberdeen, AB25 2ZN, UK
[f] Respiratory Medicine Unit, Royal Infirmary of Edinburgh, EH16 4SA, UK
[g] Department of Respiratory Medicine, Raigmore Hospital, Inverness, IV2 4AG, UK
[h] Respiratory Medicine, Perth Royal Infirmary, PH1 1NX, UK

ARTICLE INFO

Keywords:
FeNO
Asthma
Type 2 Inflammation

ABSTRACT

Fractional exhaled nitric oxide (FeNO) is the only available point of care test to assess type-2 inflammation in asthma. In making a diagnosis of asthma, FeNO should be used together with blood eosinophils and spirometry, alongside a history. Raised FeNO in conjunction with blood eosinophilia are treatable traits of type 2 inflammation in asthma, which in turn may guide personalised management. A FeNO suppression test can be used to assess adherence and device use with ICS therapy. Furthermore FeNO may be used to provide feedback to patients in response to ICS, especially when spirometry is normal. FeNO may facilitate appropriate referral to secondary care for more definitive specialist investigations. In summary, FeNO is cost effective in the diagnosis and management of asthma and should be incorporated into primary and secondary care as part of routine clinical practice.

1. Introduction

Asthma is characterised by the presence of reversible airway obstruction and airway hyper-responsiveness (AHR) usually resulting from type-2 (T2) inflammation [1] (Fig. 1). Assessment of asthma control is conventionally based on a combination of symptoms, exacerbations, reliever use and pulmonary function tests. However, in many patients these parameters are often disconnected from the underlying airway inflammatory process [2]. Optimising suppression of T2 inflammation by using sputum eosinophils to adjust the inhaled corticosteroid (ICS) dose has shown to reduce frequency of asthma exacerbation [3]. Indeed the same has been shown for suppression of AHR [4,5]. However, using induced sputum to guide treatment decisions is not feasible for routine clinical practice in either primary or secondary care. The fractional exhaled breath nitric oxide (FeNO) is a well-recognised non-invasive point of care surrogate test for T2 airway inflammation [6].

Although both FeNO and eosinophils are part of the T2 inflammatory cascade, the two biomarkers are regulated by different inflammatory pathways [7–9]. The activation of the T2 inflammatory cascade produces a variety of cytokines including interleukin-13 (IL-13) which in turn induces nitric oxide synthase in bronchial epithelium [10]. The FeNO level is related to bronchial eosinophilic inflammation [11] as well as to AHR [12].

The purpose of the present article is to produce a brief evidenced based Scottish consensus statement on the role and the utility of FeNO in adult asthma. This paper was prepared in collaboration after a meeting of all authors to discuss the relevant literature and way forwards on the role of FeNO testing, including in primary care, where its use has thus far been minimal.

1.1. FeNO as an aide to asthma diagnosis

Asthma is a clinical diagnosis, supported where possible by evidence of reversible airflow obstruction and/or airway inflammation. As such FeNO alone cannot be used to diagnose asthma. Recent asthma guidelines incorporated FeNO (≥40 ppb) as a starting point for the diagnostic algorithm, in conjunction with a comprehensive clinical history suggestive of asthma, as well as evidence of airflow obstruction ideally using spirometry [13], or where this is not available in primary care

* Corresponding author. Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, DD19SY, Scotland, UK.
E-mail address: b.j.ipworth@dundee.ac.uk (B. Lipworth).

https://doi.org/10.1016/j.rmed.2019.07.010
Received 14 December 2018; Received in revised form 14 June 2019; Accepted 5 July 2019
Available online 06 July 2019
0954-6111/

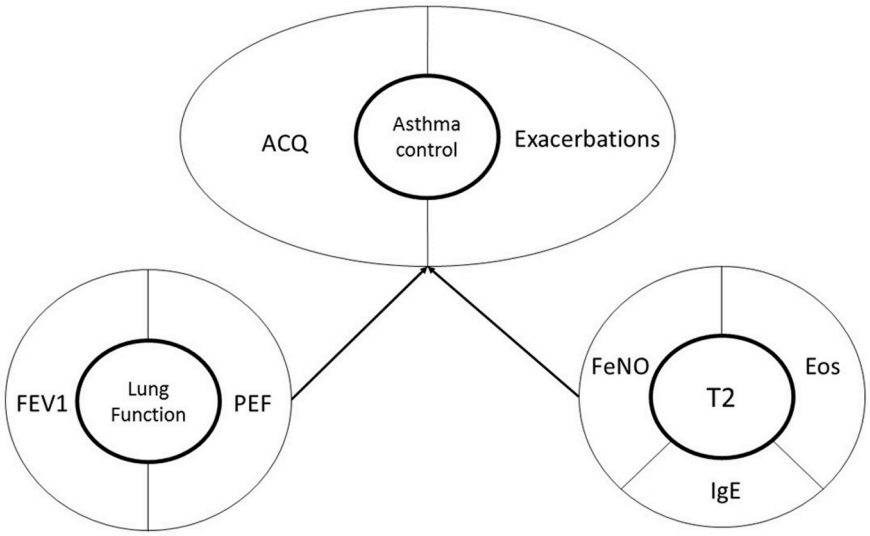

Fig. 1. Schematic diagram showing the inter-relationship between type-2 (T2) biomarkers, lung function and asthma control.

using peak expiratory flow. However, elevated FeNO levels may be especially useful at ruling in asthma in patients with a suggestive history who have normal spirometry and no bronchodilator response, as reversibility testing with salbutamol is only informative in patients with an abnormal FEV1 where there is room for improvement. Hence measuring airway calibre using spirometry and T2 inflammation using FeNO could be viewed as being relatively disconnected. Pointedly, FeNO has a higher sensitivity and specificity than measuring airway calibre using the specialist test impulse oscillometry in distinguishing preschool children with probable asthma [14]. The presence of blood eosinophilia (> 300 cells/μl) may be used to identify activity of T2 inflammation, although it may be normal in patients with raised sputum eosinophils. While FeNO alone provides sufficient accuracy for detecting T2 inflammation, the combination of FeNO and blood eosinophils further improves the strength of identifying T2 related inflammation in asthma [15]. By the same token a normal FeNO level in a patient who has stopped pre-existing ICS may be useful for undiagnosing asthma, especially when a normal value is obtained in conjunction with a negative bronchial challenge test [16].

FeNO has a steep dose response curve to budesonide reaching a plateau effect beyond 400 μg [17]. On the other hand, eosinophilic cationic protein (ECP) a marker of eosinophil activation, reaches a plateau at 800 μg, while AHR requires 1600 μg to achieve maximal suppression. Lung function measurement with spirometry (FEV1) is rather distant from the underlying T2 inflammation with no further improvement above 400 μg of budesonide [17]. Therefore, FeNO stands out as the only available non-invasive point of care test that is able to provide an objective assessment of airway inflammation in asthma.

It is also important to consider the patient's smoking status when interpreting the results as this can suppress FeNO levels [18]. FeNO levels can be elevated for other reasons such as concomitant allergic rhinitis [19] and nasal polyposis [20]. For these reasons, FeNO should be used in conjunction with blood eosinophils and spirometry, alongside a history suggesting asthma. We suggest pragmatic cut off values for FeNO of > 40 ppb and > 25 ppb to support a diagnosis of asthma in adult patients who are ICS naïve or taking ICS respectively.

1.2. FeNO to guide ICS treatment and assess adherence

ICS are the mainstay of treatment for the T2 inflammatory component of persistent asthma. A better understanding of T2 inflammation has helped clinicians to personalise asthma treatment, which in turn results in improved symptoms, exacerbations and asthma control over and above standard of care. Anderson et al. [21] demonstrated rapid improvements in FeNO after 2 days with near maximal suppression after 7 days on fluticasone propionate 100 μg/day in steroid-naïve patients. It also took approximately 5 days to wash out the effect of ICS, with FeNO returning to baseline after this point. As well as producing dose related suppression of FeNO with ICS, the asthma control questionnaire (ACQ) score showed commensurate significant improvements exceeding the minimal clinically important difference of 0.5 with mean absolute values in keeping with optimal control (< 0.75)[21]. In regards to T2 inflammation, a medium dose of ICS suppresses both FeNO and blood eosinophils respectively as well as improving AHR [22,23]. Hence, elevated FeNO may be useful to rule in asthma in patients who have stopped their pre-existing ICS.

Following a month of treatment, fluticasone propionate 200 μg/day produced 45% FeNO suppression from baseline in moderate persistent asthma, and a 77% reduction in sputum eosinophils, although the variability was much higher with the latter [24]. In regards to the effect of medium dose ICS treatment in ICS naïve patients, the improvement in ACQ was significant and almost clinically relevant, with mean change of 0.49 in patients who had a high FeNO (≥ 50 ppb) at baseline [25]. As a result of these findings and other work a recent meta-analysis [26] concluded that exacerbations were reduced by 40% in patients where FeNO was incorporated into asthma management when compared to standard care.

Non-adherence to ICS treatment is a common contributing factor to poor asthma control. FeNO has a role in monitoring response to ICS and provides an objective clinical point of care test to identify non-adherence. McNichol et al. [27] showed a relatively greater reduction in FeNO in non-adherent patients following 7 days of directly observed ICS treatment, as compared to a group of known adherent patients. A further study from the same group in severe uncontrolled asthma patients using the combination of remote FeNO and electronic inhaler monitoring showed that suppression of FeNO was similar after 1 and 4 weeks of ICS treatment, with concomitant suppression of blood eosinophils and improvements in FEV1 and ACQ [28]. This 'FeNO suppression test' can be therefore used to monitor the adherence to ICS, perhaps by bringing patients back to the clinic at regular intervals after educational input perhaps along with electronic inhaler monitoring. Moreover, the FeNO suppression test might be useful to identify non adherent patients on high dose ICS/LABA before considering expensive treatment with biologics.

Box 1

Panel consensus on utility of FeNO.

- In making a diagnosis of asthma, FeNO should be used in conjunction with blood eosinophils and spirometry, alongside a history suggesting asthma.
- Raised FeNO in conjunction with blood eosinophilia should be regarded as treatable traits of type 2 inflammation in asthma, which in turn may be used to guide personalised management decisions.
- ICS should be stopped for at least 1 week in order to obviate a false negative test for asthma when using FeNO.
- We suggest pragmatic cut off values for FeNO of > 40 ppb and > 25 ppb to support a diagnosis of asthma in adult patients who are ICS naïve or taking ICS respectively.
- Serial FeNO measures, the so called FeNO suppression test, can be used to help assess adherence and device use with ICS therapy.
- FeNO may be useful as a tool to provide feedback and reassurance to patients in response to ICS, especially in cases where spirometry is normal.
- FeNO may be used to facilitate appropriate referral to secondary care for more definitive specialist investigations such as bronchial challenge testing.
- FeNO is cost effective in the diagnosis and management of asthma and should be incorporated into primary care as part of routine clinical practice.

1.3. FeNO and biologic therapy

With increasing use of biologic therapy in asthma we believe it is important for primary and secondary care physicians to have a basic understanding of the potential role of FeNO in the management of severe asthma. Current asthma guidelines advocate that biologic agents should be considered for poorly controlled frequently exacerbating patients including those who require maintenance oral corticosteroids [29–31]. Thus it is important to consider which biomarkers can be employed to target T2 inflammation with appropriate biologics including anti-IgE (omalizumab), anti-IL 5 (mepolizumab, reslizumab or benralizumab) or anti-IL4/13 (dupilumab). In other words can biomarkers including FeNO be used to personalise biologic therapy. A key point to bear in mind is that FeNO is mediated by IL-13 signalling while eosinophils are mediated by IL-5.

The EXTRA study [32] evaluated the additional benefit of omalizumab in reducing future asthma exacerbations in uncontrolled severe persistent allergic asthma despite treatment with ICS/LABA. Use of omalizumab was associated with 25% relative overall reduction in asthma exacerbations compared to placebo [32]. A pre-specified post hoc analysis showed that a greater reduction in asthma exacerbations was seen in the high FeNO group (> 19.5 ppb) with a mean reduction of 53% compared to 16% in the low FeNO group (< 19.5ppb) [32] Therefore, use of FeNO may help to identify the patients who are likely to benefit most from treatment with omalizumab.

Mepolizumab which blocks IL-5 signalling reduces exacerbations compared to placebo in patients with severe eosinophlic asthma despite there being no concomitant effect on FeNO, in keeping with the known effects of IL-5 on eosinophils but not FeNO [33].

Dupilumab acts by blocking the IL-4 receptor α and hence inhibits signalling of both IL-4 and IL-13, which are key drivers of T2 inflammation. Dupilumab was found to optimally reduce exacerbations and improve FEV1 in patients who exhibited both FeNO > 25 ppb and blood eosinophils > 150 cell/ul [34]. Furthermore, dupilumab produced significant reductions in FeNO levels on top of pre-existing medium to high dose ICS, in keeping with the known effects of IL-13 on FeNO. Therefore, FeNO is a reliable T2 biomarker for predicting improvements in airway calibre and reduction in asthma exacerbation mediated by blocking IL-4/13. In another study in oral corticosteroid dependent severe asthma, FeNO was significantly reduced even in association with tapering down the dose of oral glucocorticoid while patients were receiving dupilumab treatment comparing to placebo [35].

A randomised placebo-controlled trial that evaluated the effect of anti-IL 13 therapy with tralokinumab [36] showed significant reduction in FeNO despite there being no significant reduction on blood, bronchial mucosal or sputum eosinophils [36]. This again showed the disconnection between IL-13 mediated effects on FeNO and eosinophils.

1.4. Health economics of FeNO

Asthma diagnosis based on FeNO measurement with NIOX MINO is less costly and more accurate than standard diagnostic methods. Utilisation of FeNO measurement in asthma diagnosis cost £43 less per patient as compared with standard diagnostic tests such as spirometry [37]. This resulted in annual cost-savings of £341 and 0.06 quality-adjusted life-years gained for patients with mild to severe asthma along with £544 and 0.004 quality-adjusted life-years gained for those with moderate to severe asthma [37]. A primary care study showed that a FeNO driven strategy for asthma control achieves the highest probability of cost effectiveness in terms of willingness to pay to achieve a quality of life adjusted year [38].

1.5. Conclusions (Box 1)

FeNO is the only non-invasive point of care test to assess type 2 inflammation in asthma. FeNO appears to be a cost effective way of making an asthma diagnosis and in achieving better control with ICS therapy. FeNO and blood eosinophils should be used together as treatable traits of type 2 inflammation in asthma to guide informed management decisions on a personalised basis. The use of FeNO will continue to evolve in a primary care setting and will depend on availability and accessibility within different regions. A hub and spoke approach linking several practices with a FeNO machine might be a cost effective way forward for primary care to more widely adopt this test.

Author contributions

All of the authors who were present at the meeting had an input into writing the paper. Dr Kuo and Dr Lipworth wrote the first draft of the manuscript. Dr Kuo, Dr Lipworth, Dr Spears, Dr Haughney, Dr Smith, Dr Miller, Dr Bradshaw, Dr Murray and Dr Williamson were responsible for the review and final version the manuscript.

Conflicts of interest

Dr. Kuo reports personal fees from Circassia, during the conduct of the study; personal fees from Pfizer/Bristol-Myers Squibb, outside the submitted work.

Dr. Spears reports personal fees from Circassia, during the conduct of the study. Dr. Haughney reports personal fees from Circassia, during the conduct of the study. Dr. Smith reports personal fees from Circassia,

during the conduct of the study.

Dr. Miller reports personal fees from Circassia, during the conduct of the study.

Dr. Bradshaw reports personal fees from Circassia, during the conduct of the study; personal fees from Novartis, personal fees from Novartis, personal fees from Chiesi, personal fees from Astrazeneca, outside the submitted work.

Dr. Murray reports personal fees from Circassia, during the conduct of the study; non-financial support from Chiesi, personal fees from Scottish Allergy and Respiratory Academy, non-financial support from European Respiratory Society, outside the submitted work.

Dr. Williamson reports personal fees from Circassia, during the conduct of the study.

Dr. Lipworth reports grants and personal fees and grants from AstraZeneca , personal fees and other from Teva, personal fees from Novartis, personal fees from Sanofi, grants and personal fees from Chiesi, personal fees and non-financial support from Circassia, during the conduct of the study; grants and personal fees from Meda, grants from Janssen, grants from Roche, personal fees from Lupin, grants and personal fees from Boerhinger Ingelheim, personal fees from Cipla, personal fees from Sandoz, personal fees from Dr Reddys, personal fees from Thorasys, non-financial support from GSK, outside the submitted work; and the son of BJL is an employee of AstraZeneca.

Acknowledgements

The authors would like to thank Circassia Ltd (Oxford, UK) for providing an unrestricted educational grant to support the meeting in Perth on 9th October 2018 which formed the basis of this manuscript. Circassia were not present at the meeting and had no input into preparation of the manuscript. All of the authors who were present at the meeting had an input into writing the paper.

References

[1] Global Initiative for Asthma 2018 Guidelines, https://ginasthma.org/ , Accessed date: 13 December 2018.
[2] A.M. Vignola, P. Chanez, A.M. Campbell, et al., Airway inflammation in mild intermittent and in persistent asthma, Am. J. Respir. Crit. Care Med. 157 (2) (1998) 403–409.
[3] R.H. Green, C.E. Brightling, S. McKenna, et al., Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial.[see comment], Lancet 360 (9347) (2002) 1715–1721.
[4] B.J. Lipworth, P.M. Short, P.A. Williamson, et al., A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial, Chest 141 (3) (2012) 607–615.
[5] J.K. Sont, L.N. Willems, E.H. Bel, et al., Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group, Am. J. Respir. Crit. Care Med. 159 (4 Pt 1) (1999) 1043–1051.
[6] I.D. Pavord, S. Afzalnia, A. Menzies-Gow, L.G. Heaney, The current and future role of biomarkers in type 2 cytokine-mediated asthma management, Clin. Exp. Allergy 47 (2) (2017) 148–160.
[7] A. Malinovschi, J.A. Fonseca, T. Jacinto, K. Alving, C. Janson, Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects, J. Allergy Clin. Immunol. 132 (4) (2013) 821–827 e821-825.
[8] J. Corren, R.F. Lemanske, N.A. Hanania, et al., Lebrikizumab treatment in adults with asthma, N. Engl. J. Med. 365 (12) (2011) 1088–1098.
[9] P. Haldar, C.E. Brightling, B. Hargadon, et al., Mepolizumab and exacerbations of refractory eosinophilic asthma, N. Engl. J. Med. 360 (10) (2009) 973–984.
[10] K. Chibana, J.B. Trudeau, A.T. Mustovich, et al., IL-13 induced increases in nitrite levels are primarily driven by increases in inducible nitric oxide synthase as compared with effects on arginases in human primary bronchial epithelial cells, Clin. Exp. Allergy 38 (6) (2008) 936–946.
[11] D.N. Payne, I.M. Adcock, N.M. Wilson, et al., Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone, Am. J. Respir. Crit. Care Med. 164 (8 Pt 1) (2001) 1376–1381.
[12] A. Jatakanon, S. Lim, S.A. Kharitonov, K.F. Chung, P.J. Barnes, Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma, Thorax 53 (2) (1998) 91–95.
[13] National Institute for Health and Care Excellence, Asthma: Diagnosis, Monitoring and Chronic Asthma Management (NG80), (2017) https://www.nice.org.uk/guidance/ng80/resources/asthma-diagnosis-monitoring-and-chronic-asthma-management-pdf-1837687975621 , Accessed date: 17 October 2018.
[14] L.P. Malmberg, A.S. Pelkonen, T. Haahtela, M. Turpeinen, Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma, Thorax 58 (6) (2003) 494–499.
[15] Y. Colak, S. Afzal, B.G. Nordestgaard, J.L. Marott, P. Lange, Combined value of exhaled nitric oxide and blood eosinophils in chronic airway disease: the Copenhagen General Population Study, Eur. Respir. J. 52 (2) (2018).
[16] B.J. Lipworth, S. Jabbal, Un-diagnosing persistent adult asthma, Eur. Respir. J. 50 (5) (2017).
[17] A.M. Wilson, B.J. Lipworth, Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma, Am. J. Med. 108 (4) (2000) 269–275.
[18] K.L. Clearie, L. McKinlay, P.A. Williamson, B.J. Lipworth, Fluticasone/Salmeterol combination confers benefits in people with asthma who smoke, Chest 141 (2) (2012) 330–338.
[19] C. Gratziou, M. Lignos, M. Dassiou, C. Roussos, Influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis, Eur. Respir. J. 14 (4) (1999) 897–901.
[20] J. Galli, P. Montuschi, G.C. Passali, et al., Exhaled nitric oxide measurement in patients affected by nasal polyposis, Otolaryngol. Head Neck Surg. 147 (2) (2012) 351–356.
[21] W.J. Anderson, P.M. Short, P.A. Williamson, B.J. Lipworth, Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial, Chest 142 (6) (2012) 1553–1561.
[22] W.J. Anderson, P.M. Short, S. Jabbal, B.J. Lipworth, Inhaled corticosteroid dose response in asthma: should we measure inflammation? Ann. Allergy Asthma Immunol. 118 (2) (2017) 179–185.
[23] S. Jabbal, B.J. Lipworth, Blood eosinophils: the forgotten man of inhaled steroid dose titration, Clin. Exp. Allergy 48 (1) (2018) 93–95.
[24] G.P. Currie, K. Haggart, J.D. Brannan, et al., Relationship between airway hyperresponsiveness to mannitol and adenosine monophosphate, Allergy 58 (8) (2003) 762–766.
[25] D.B. Price, R. Buhl, A. Chan, et al., Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial, The Lancet. Respiratory medicine 6 (1) (2018) 29–39.
[26] H.L. Petsky, C.J. Cates, K.M. Kew, A.B. Chang, Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis, Thorax 73 (12) (2018) 1110–1119.
[27] D.M. McNicholl, M. Stevenson, L.P. McGarvey, L.G. Heaney, The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma, Am. J. Respir. Crit. Care Med. 186 (11) (2012) 1102–1108.
[28] L.G. Heaney, J. Busby, P. Bradding, et al., Remotely monitored therapy and nitric oxide suppression identifies non-adherence in severe asthma, Am. J. Respir. Crit. Care Med. 199 (4) (2019) 454–464.
[29] National Institute for Health and Care Excellence, Omalizumab for treating severe persistent allergic asthma, https://www.nice.org.uk/guidance/ta278/resources/omalizumab-for-treating-severe-persistent-allergic-asthma-pdf-82600619176645 , Accessed date: 17 October 2018.
[30] National Institute for Health and Care Excellence, Reslizumab for Treating Severe Eosinphilic Asthma, https://www.nice.org.uk/guidance/ta479/resources/reslizumab-for-treating-severe-eosinophilic-asthma-pdf-82604974420933 , Accessed date: 17 October 2018.
[31] National Institute for Health and Care Excellence, Mepolizumab for treating severe refractory eosinphilic asthma, https://www.nice.org.uk/guidance/ta431/resources/mepolizumab-for-treating-severe-refractory-eosinophilic-asthma-pdf-82604719119301 , Accessed date: 17 October 2018.
[32] N.A. Hanania, S. Wenzel, K. Rosen, et al., Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study, Am. J. Respir. Crit. Care Med. 187 (8) (2013) 804–811.
[33] I.D. Pavord, S. Korn, P. Howarth, et al., Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, Lancet 380 (9842) (2012) 651–659.
[34] M. Castro, J. Corren, I.D. Pavord, et al., Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma, N. Engl. J. Med. 378 (26) (2018) 2486–2496.
[35] K.F. Rabe, P. Nair, G. Brusselle, et al., Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma, N. Engl. J. Med. 378 (26) (2018) 2475–2485.
[36] R.J. Russell, L. Chachi, J.M. FitzGerald, et al., Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled phase 2 trial, The Lancet. Respiratory medicine 6 (7) (2018) 499–510.
[37] D. Price, J. Berg, P. Lindgren, An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom, Allergy 64 (3) (2009) 431–438.
[38] P.J. Honkoop, R.J. Loijmans, E.H. Termeer, et al., Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care, J. Allergy Clin. Immunol. 135 (3) (2015) 682–688 e611.