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Short review

The clinical features of asthma exacerbations in early-onset and eosinophilic late-onset asthma may differ significantly

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A B S T R A C T

Over 20 years ago, the concept of asthma control was created and appropriate measurement tools were developed and validated. Loss of asthma control can lead to an exacerbation.

Years ago, the term "clinically significant asthma exacerbation" was introduced to define when a loss of control is severe enough to declare it an asthma exacerbation.

This term is also used by health insurances to determine when an exacerbation is eligible for reimbursement of biologics in clinical practice, however, it sometimes becomes apparent that a clear separation between loss of "asthma control" and an exacerbation is not always possible.

In this review, we attempt to justify why exacerbations in early allergic asthma and adult eosinophilic asthma can differ significantly and why this is important in clinical practice as well as when dealing with health insurers.

1. Eosinophilic type 2 asthma consists of two different phenotypes of the disease

The literature regarding *asthma control* and *exacerbations* mainly dates back to 2010 and before, implying that there is an orientation towards T helper 2 (TH2) asthma, i.e. *allergic asthma*. After the discovery of the TH2 allergic-pathway in the 1980s, the view dominated that an allergic reaction underlies every type of asthma, even if no obvious sensitization to aeroallergens was detectable [1].

Yet, a predominantly non-allergic *eosinophilic adult-onset asthma* type was first described as far back as 1918 [2] and subsequently termed *Intrinsic Asthma* in 1947 by the same author [3]. A rethinking has only occurred in recent years due to two factors: First, the pharmaceutical industry introduced anti-IL5 monoclonal antibodies that effectively reduced the number of eosinophilic granulocytes with an effect on asthma symptoms that is detectable mainly in patients with blood eosinophilia [4]. Second, these responders more often belonged to a distinct group of patients in whom asthma had manifested during adulthood with the presence of an atopy status similar to the average normal population [5]. This type of eosinophilic inflammation can occur in the absence of an allergic reaction to aeroallergens and originates from innate lymphocytic cells (ILC) [6]. Asthma, based on an eosinophilic inflammation involving Interleukin (IL) 4, IL5, and IL13 with resulting blood eosinophilia and/or elevated exhaled nitric oxide

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(FeNO), is nowadays called *Type 2 asthma* [7].

2. Asthma treatment presently depends on the assessment of the degree of asthma control and recognition of an asthma exacerbation

Asthma control and asthma exacerbation are two distinct terms to better describe the clinical features of asthma and to assess the necessity of further treatment. The idea of *asthma control* was introduced more than two decades ago and different composite scores were validated in the meantime. These are all based on specific questions regarding asthma symptoms in the preceding week or month, and integration of FEV_1 for one of them [8–10].

Asthma control was defined as the extent to which the various manifestations of asthma are reduced or removed by treatment [11]. Poor asthma control correlates with increased peak flow-variability [12] and one of the most commonly reported lung function variable was morning peak flow rate (PEFR) prior to bronchodilator treatment. Insufficient asthma control most often requires a long-term adjustment of therapy.

According to the ATS/ERS statement of 2009, *asthma exacerbations* (flare-ups) correspond to a loss of asthma control and should be clinically identified by changes in symptoms, which are outside the patient's usual range of day-to-day variation [11]. A severe exacerbation was defined by the requirement of a corticosteroid burst of at least 3 days, after which the treatment can resume with the prior daily dose of asthma medication in most cases.

As mentioned above, 20 years ago the scientific view was focused mainly on allergic asthma. This explains why the symptoms employed to assess asthma control correlate with the degree of bronchial hyperresponsiveness, a typical feature of allergic asthma being uncontrolled due to allergen exposure. In allergic asthma, exacerbations often occur with a short latency, triggered by a viral airway infection, a substantial exposure to allergens, or a combination of both [13]. Today, GINA defines asthma exacerbation as an acute or subacute worsening of symptoms and lung function compared to the patient's usual status [8]. In the German S2k guideline, an exacerbation is described as a phase of progressive increase in asthma symptoms and/or decrease in lung function [14]. In 2009, the aspect of lung function decline was not yet part of the definition of an asthma exacerbation [11].

The recognition and treatment of an exacerbation in severe asthma is not only important for the patient from a short term perspective, but is also crucial in the long-term because, apart from a significant blood eosinophilia, it is the annual rate of exacerbations that poses the indication for a treatment with biologics to avoid longer term systemic corticosteroids.

In contrast to the recent definitions of exacerbations, medical advisors of health insurances often interpret exacerbations as an abrupt worsening with intense asthma symptoms. This may, however, not be the case in eosinophilic adult-onset asthma, often rendering the negotiations for reimbursement of a treatment with biologics more challenging.

3. Differences in symptomatology of early-onset and late-onset asthma

One of the first cluster analyses to prospectively identify asthma phenotypes clearly indicated that in eosinophilic adult-onset asthma discordance exists between the extent of eosinophilic inflammation and typical asthma symptoms [15] (Fig. 1). These typical asthma symptoms being evaluated with asthma control questionnaires signify bronchial hyperresponsiveness with an increase in daily variability of Peak flow rate (PEFR) [12] respectively low FEV_1-values in the morning (*morning dipping* [16]) and loss of asthma control. This feature is most often observed in allergic early-onset asthma.

In the above mentioned and other cluster analyses, patients with eosinophilic late-onset asthma had fewer asthma symptoms related to an increase in bronchial muscle tone, despite severe eosinophilic inflammation. When exacerbating, these patients instead develop a productive cough, increasing mucosal swelling, and mucus plugging of the bronchi leading to a bronchial obstruction that is not reversible with bronchodilators. Consecutively, a loss of FEV_1 after bronchodilation appears that responds only to adequate doses of corticosteroids. Thus, such clinical picture with absence of sudden acute asthma attacks and decline of FEV_1 without reversibility to bronchodilators may mimic fixed airway obstruction typical of COPD [17].

The clinical picture of early-onset and late-onset asthma can therefore differ substantially [18], and hence publications from more than a decade ago on asthma exacerbations must now be regarded as being partially incomplete. Asthma exacerbations are therefore not generally to be equated with acute asthma attacks predominating in early-onset

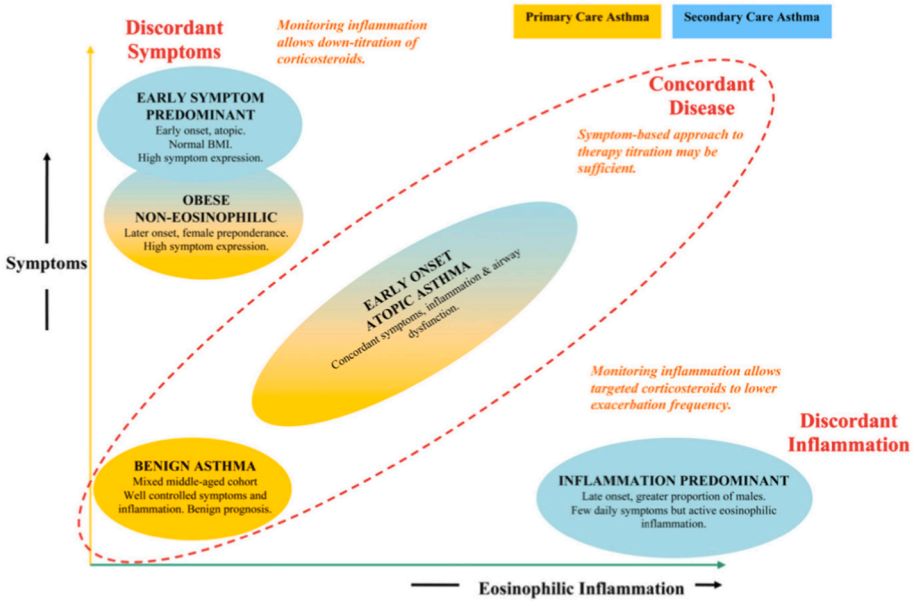

Fig. 1. Discordance of eosinophilic inflammation and typical asthma symptoms (reprint from ref. [15]).

asthma with bronchial hyperresponsiveness and consecutive bronchospasm. The latency from onset to clinical relevance of an asthma exacerbation can be short, but may also take weeks [19].

4. Two different peak flow patterns reveal the loss of asthma control, respectively an exacerbation

As early as 1977, Dame Turner-Warwick noticed that worsening of asthma control did not always increase variability of PEFR, but that in some cases PEFR decreased consecutively over time with no apparent improvement in spontaneous values during the day or after inhalation of a bronchodilator. She called this the *drifter-type* [16] of asthma.

In 1999, an analysis of peak flow protocols in asthma patients by Reddel et al. confirmed that exacerbations were often accompanied by a continuous decrease in PEFR values without reversibility to bronchodilators [20]. The authors attributed this to viral infections, although rhinoviruses had not been searched for. It may therefore be assumed that some of these patients exacerbated spontaneously because the dose of anti-inflammatory medication taken was below the individual threshold dose needed to inhibit a spontaneous flare up of Type 2 inflammation.

With fading corticosteroid action after a burst, typical asthma symptoms are often lacking in eosinophilic late-onset asthma despite marked eosinophilic inflammation. In such a situation, a slowly progressive exacerbation rather than an acute asthma attack will appear, causing exertional dyspnoea and bronchial obstruction that is not reversible with bronchodilator treatment. In addition, nasal congestion and rhinorrhoea can occur because Type 2 inflammation often manifests itself in the upper airways too. In the absence of a differential blood cell count showing eosinophilia, such symptoms may lead to the incorrect clinical diagnosis of a virus-induced exacerbation resulting in a brief corticosteroid burst, rather than the indication for a long-term adjustment of anti-inflammatory asthma therapy.

As mentioned in the 2009 ATS/ERS-Statement, the terms asthma control and exacerbation should be clearly differentiated. Inadequate asthma control over a certain period means that the daily dosage of drugs is insufficient to treat the disease adequately. In contrast, an exacerbation defines a transient loss of asthma control, most often due to viral infection and/or sudden allergen exposure requiring transient intensification of the therapy to regain again asthma control with the former drug regime.

Can these definitions be completely adopted for eosinophilic adult-onset asthma? In this context, asthma is well controlled when Type 2 inflammation is adequately treated. However, tapering of oral corticosteroids (OCS) or inhaled corticosteroids (ICS) below the individually needed threshold dose will not lead to a permanent state of partly controlled asthma. Most often it will provoke a progressive exacerbation that may become moderate or even severe. This type of response epitomises the limits of the commonly utilised definitions on asthma control and exacerbations.

5. Necessity to treat a loss of post-bronchodilation FEV_1 in type 2 inflammation

Despite the presence of subacute symptoms only, diagnosis and treatment of a slowly progressive FEV_1 decline is necessary to prevent permanent loss of lung function and ultimately permanent airway remodelling [21], which becomes clinically apparent with COPD-like features in lung function testing. Generally, a short corticosteroid burst followed by an increase in the daily dose of asthma medication is necessary to treat a slowly progressive FEV_1 decline. In contrast, in previously controlled early-onset asthma, the initial dosage of medication prior to the burst can most often be maintained thereafter.

As early as 1989, Ann Woolcock [22], in a publication that formed the basis for the later GINA asthma guidelines, therefore pointed out the importance of knowing a patient's *individual best* FEV_1 (or alternatively PEFR) and using such baseline value as a therapeutic goal to be maintained during further therapy. Although GINA guidelines also recommended regular monitoring of FEV_1 to assess asthma control, this item was removed only a few years ago, most likely in order to render the GINA asthma control assessment globally applicable in countries with restricted health care resources and limited access to spirometry.

6. The *individual best* FEV_1 is essential to identify an exacerbation in severe eosinophilic asthma

In early-onset allergic asthma, an asthma exacerbation can easily be recognised by the appearance of typical asthma symptoms. In contrast, late-onset eosinophilic asthma exacerbations often occur due to the fact, that anti-inflammatory medication is not sufficient anymore to suppress a spontaneous flare-up of Type 2 inflammation. In such a context, the development of an exacerbation will often be slow and less associated with typical asthma symptoms, as compared to early-onset asthma.

Therefore, in the presence of a relevant decline of post-bronchodilator FEV_1 compared to the *individual best* value, combined with signs of an active Type 2 inflammation (increased blood eosinophils and/or FeNO), an exacerbation has occurred, requiring a systemic corticosteroid burst and a consecutive intensification of the daily anti-inflammatory therapy. As this type of asthma is frequently associated with ICS resistance [23], a further increase of the ICS dose may be insufficient, necessitating treatment with daily OCS respectively biologics. Without adequate treatment of Type 2 inflammation, the risk of developing permanent airway remodelling and the risk of further worsening potentially leading to a life-threatening exacerbation increases, as it often has occurred in the pre-corticosteroid era [24].

Of note, a single corticosteroid burst may suppress bone formation for up to three months due to an attenuation of osteoblast activity, causing bone loss and development of osteoporosis [25,26]. Osteoporotic fractures of thoracic vertebrae lead to a restrictive lung function pattern increasing exertional dyspnoea.

It must be emphasized that in former studies, whenever PEFR, respectively FEV_1 were monitored, the focus was on morning values *prior* to bronchodilator treatment to detect an increase of Peak Flow variability associated with bronchial hyperresponsiveness. However, to detect inflammatory mucosal swelling and mucus plugging of distal airways, in adult-onset asthma *post* bronchodilator FEV_1 values are more relevant to determine lung functional impairment in relation to the individual best value [21,27].

We consider that it is important to address these clinical differences between the two asthma phenotypes in future studies. In addition, active and ex-smokers with fixed airway obstruction should also be screened for Type 2 inflammation. In a first work-up, a complete differential blood cell count and a measurement of FeNO are necessary taking into consideration that active smoking may generate false negative FeNO values.

7. What qualifies an asthma exacerbation as being clinically significant?

Already decades ago, the importance of monitoring eosinophilia in non-allergic eosinophilic and in allergic asthma with dominating eosinophilic late-reaction was emphasized [28]. Corticosteroid reduction studies have consistently shown that a raised sputum or blood eosinophil count in asthma is predictive for the development of an exacerbation [29,30], ultimately causing a bronchial obstruction that is unresponsive to bronchodilation. Therefore, optimal control of this asthma phenotype should not only include a symptom score, but also

incorporate a differential blood cell count, and spirometry to enable comparison of current post bronchodilator FEV_1 with the individual best value.

Health insurances only grant reimbursement for biologics in severe eosinophilic asthma if a relevant blood eosinophilia is detectable and *clinically significant* asthma exacerbations occur several times a year.

What magnitude of decline in post-bronchodilator FEV_1 compared to the individual best value defines a significant exacerbation? Even a repeatedly measured small FEV_1 decline may indicate a clinically relevant exacerbation in the presence of increased Type 2 inflammatory markers (FeNO and/or blood eosinophilia). Further deterioration is likely to occur in the individual patient if no action is taken.

We consider a 10% decline as being significant on the basis of former studies showing that the minimal important difference (MID) for improvement and worsening in FEV_1 is about 10%, based on patient perception of change [31,32].

Regarding PEFR, there exists already a number that relates to the decrease in lung function: the study showed that in severe eosinophilic asthma, a drop in PEFR of just 77 L/min post bronchodilator correlates with 3 or more annual exacerbations. However, this number refers to the proportion of fixed airway obstruction, not unequivocally to the decrease from the individual best PEFR, which could theoretically be reversed by a corticosteroid burst [33].

Another parameter to describe the clinical significance of an exacerbation is based on the duration of a systemic corticosteroid burst that is required to adequately treat an exacerbation. In the ATS/ERS-Statement and the anti-IL5 antibody trials, an oral corticosteroid administration of at least three days was almost universally defined as the minimal necessary therapeutic intervention [11,34].

8. Summary

Dissimilar symptoms between early-onset asthma and eosinophilic adult-onset asthma frequently cause different clinical presentations of exacerbations. In early-onset asthma an increase in typical asthma symptoms will appear eventually leading to an asthma attack. This contrasts with eosinophilic adult-onset asthma, where slowly progressive symptoms such as cough, phlegm, and exertional dyspnea coincide with the onset of bronchial obstruction that is non-responsive to bronchodilation. Such a protracted course of an exacerbation can be identified by a gradual decline in post bronchodilator FEV_1 as compared to the individual best value, justifying a transient systemic corticosteroid burst.

Conflicts of interest of the authors

Dr. Rothe was member of Advisory Boards of Vifor, Novartis, GSK, and AstraZeneca. He held lectures for AstraZeneca, Vifor, Glaxo, Sanofi, and OM Pharma.

Prof. Dr. Brideveaux held lectures for Boehringer, Sanofi, and Novartis.

Prof. Dr. von Garnier held lectures for Sanofi, AstraZeneca, Boehringer, GSK, Mundipharma, Novartis, and Pfizer.

Dr. Clarenbach has been member of Advisory Boards of GSK, Novartis, Vifor, Boehringer, AstraZeneca, Sanofi and Daiichi Sankyo and held lectures for GSK, Novartis, Vifor, Boehringer, AstraZeneca, and Sanofi.

Dr. Charbonnier received consulting fees from GSK and Sanofi, held lectures for GSK, Sanofi, AstraZeneca, and Novartis. He participed in Advisory Boards of Sanofi and AstraZeneca.

Dr. Gianella held lectures for Sanofi and GSK. He was member of an Advisory Board of Novartis.

Dr. Kern participed in Advisory Boards of GSK, Sanofi, and AstraZeneca.

Dr. Jochmann did not declare any conflicts of interest.

Dr. Pavlov held lectures for AstraZeneca, CSL Behring, GSK, Novartis, Olympus, OM Pharma, and Sanofi. He was member of Advisory Boards of AstraZeneca, GSK, Novartis, OM Pharma, and Sanofi.

Prof. Dr. Steurer-Stey received Consulting Fees from Boehringer, Sanofi, and Novartis. She held lectures for AstraZeneca, OM Pharma, GSK, and Novartis.

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References

[1] M. Humbert, J.A. Grant, L. Taborda-Barata, et al., High-affinity IgE receptor (Fc-epsilonRI)-bearing cells in bronchial biopsies from atopic and nonatopic asthma, Am. J. Respir. Crit. Care Med. 153 (1996) 1931–1937.
[2] F.M. Rackemann, A clinical study of one hundred and fifty cases of bronchial asthma, Arch. Intern. Med. 22 (1918) 517–523.
[3] F.M. Rackemann, Intrinsic asthma, Bull. N. Y. Acad. Med. 5 (1947) 302–306.
[4] P. Haldar, C.E. Brightling, B. Hargadon, et al., Mepolizumab and exacerbations of refractory eosinophilic asthma, N. Engl. J. Med. 360 (2009) 973–984.
[5] M. Amelink, J.C. de Groot, S.B. de Nijs, et al., Severe adult-onset asthma: a distinct phenotype, J. Allergy Clin. Immunol. 132 (2013) 336–341.
[6] G. Brusselle, T. Maes, K. Bracke, Eosinophils in the spotlight: eosinophilic airway inflammation in non-allergic asthma, Nat Med 19 (2013) 977–979.
[7] D. Robinson, M. Humbert, R. Buhl, et al., Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications, Clin. Exp. Allergy 47 (2017) 161–175.
[8] www.ginasthma.org. (Accessed 17 August 2022).
[9] E.F. Juniper, P.M. Byrne, G.H. Guyatt, et al., Development and validation of a questionnaire to measure asthma control, Eur. Respir. J. 14 (1999) 902–907.
[10] C.E. Jia, H.P. Zhang, Y. Lv, et al., The asthma control test and asthma control questionnaire for assessing asthma control: systematic review and meta-analysis, J. Allergy Clin. Immunol. 131 (2013) 695–703.
[11] H. Reddel, D.R. Taylor, E.D. Bateman, et al., An official ATS/ERS statement: asthma control and exacerbations: standardizing endpoints for asthma trials and clinical practice, Am. J. Respir. Crit. Care Med. 180 (2009) 59–99.
[12] G. Ryan, K.M. Latimer, J. Dolovich, F.E. Hargreave, Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre, Thorax 37 (1982) 423–429.
[13] J.R. Castillo, S.P. Peters, Busse WW asthma exacerbations: pathogenesis, prevention, and treatment, J. Allergy Clin. Immunol. Pract. 5 (2017) 918–927.
[14] DGP, dt. Atemwegsliga, dt. Ges. für pädiatr. Pneumologie et al, S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma: Registernummer 020-009, Version 2017-11_11. www.awmf.org/leitlinien/detail/II/020-009.html, 2017.
[15] P. Haldar, I.D. Pavord, D.E. Shaw, M.A. Berry, M. Thomas, C.E. Brightling, et al., Cluster analysis and clinical asthma phenotypes, Am. J. Respir. Crit. Care Med. 178 (2008) 218–224.
[16] M. Turner-Warwick, On observing patterns of airway obstruction in chronic asthma, Br. J. Dis. Chest 71 (1977) 73–86.
[17] H.M. Brown, Treatment of chronic asthma with prednisolone. Significance of eosinophils in the sputum, Lancet 2 (1958) 1245–1247.
[18] T. Rothe, Asthma control measures reconsidered, Respirology 26 (2021) 21–22.
[19] A.E. Tattersfield, D.S. Postma, P. Barnes, et al., Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group, Am. J. Respir. Crit. Care Med. 160 (1999) 594–599.
[20] H. Reddel, S. Ware, G. Marks, et al., Differences between asthma exacerbations and poor asthma control, Lancet 353 (1999) 364–369.
[21] S. Saglani, C.M. Lloyd, Novel concepts in airway inflammation and remodeling in asthma, Eur. Respir. J. 46 (2015) 1796–1804.
[22] A. Woolcock, A.R. Rubinfeld, J.P. Seale, et al., Thoracic society of Australia and New Zealand. Asthma management plan, Med. J. Aust. 151 (1989) 650–653.
[23] M.C. Peters, S. Kerr, E.M. Dunican, Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids, J. Allergy Clin. Immunol. 144 (2019) 104–113.
[24] U. Zoeppritz, Die Therapie des Asthmas bronchiale, Inaugurationsdissertation der Universität Tübingen, 1948.
[25] A. Rauch, S. Seitz, U. Baschant, et al., Glucocorticoids suppress bone formation by attenuating osteoblast differentiation via the monomeric glucocorticoid receptor, Cell Metabol. 11 (2010) 517–531.
[26] I.R. Skov, H. Madsen, D.P. Henriksen, et al., Low dose oral corticosteroids in asthma associates with increased morbidity and mortality, Eur. Respir. J. (2022), https://doi.org/10.1183/13993003.03054-2021.
[27] T. Rothe, A comprehensive graphic approach to peak flow traffic light-system interpretation, Eur. Respir. J. 10 (1997) 961–962.
[28] P.M. O'Byrne, F.E. Hargreave, Impact of monitoring inflammation on the management of adult asthmatic patients, Allergy 48 (1993) 153–157.
[29] N. Mallah, S. Rodriguez-Segade, F.-J. Gonzalez-Barcala, B. Takkouche, Blood eosinophil count as predictor of asthma exacerbation. A meta-analysis, Pediatr. Allergy Immunol. 32 (2021) 465–478.

[30] A. Jatakanon, S. Lim, P.J. Barnes, Changes in sputum eosinophils predict loss of asthma control, Am. J. Respir. Crit. Care Med. 161 (2000) 64–72.
[31] N.C. Santanello, J. Zhang, B. Seidenberg, et al., What are minimal important changes for asthma measures in a clinical trial? Eur. Respir. J. 14 (1999) 23–27.
[32] S.J. Szefler, R.J. Martin, T.S. King, et al., Significant variability in response to inhaled corticosteroids for persistent asthma, J. Allergy Clin. Immunol. 109 (2002) 410–418.
[33] H. Ortega, S.W. Yancey, O.N. Keene, et al., Asthma exacerbations associated with lung function decline in patients with severe eosinophilic asthma, J. Allergy Clin. Immunol. Pract. 6 (2018) 980–986.
[34] H.A. Farne, A. Wilson, C. Powell, et al., Cochrane Database Syst. Rev. 9 (2017), CD010834, https://doi.org/10.1002/14651858.CD010834.pub3. PMID: 28933516.