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Health Policy
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Colophon

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1 Introduction

Severe asthma is extremely difficult, if at all, to control with asthma medication and other treatment. As a result the disease has a strong impact on patients' everyday lives. The impact of both the disease and its treatment may have changed due to availability of new treatment options, especially the addition of new biologicals, but little is known about patients' experiences of these add-on treatments. In this study we explore the everyday life of patients with an eosinophilic phenotype of severe asthma in relation to the use of these biologicals using benralizumab as case in point.

We ask the following questions:
1) How do patients with severe asthma experience their daily life? and
2) How do patients with severe asthma experience the healthcare they receive, and specifically the use of benralizumab, within the context of their daily life?

To answer these questions, we use a non-interventional, exploratory, qualitative research design. We first conducted a literature review of relevant scientific literature. Subsequently we analysed existing patient experience stories, interviewed ten patients with severe asthma and two healthcare professionals specialized in severe asthma in the Netherlands. The patient interviews were approached as "life-histories", giving patients the opportunity to share their own experiences. We sought diversity in patients' narratives on daily life with severe asthma and the impact of biologicals, whilst ensuring a professionals' perspective through interviewing a physician and a nurse-specialist.

The aim of this study is to gain a greater understanding of the impact of treatment with biologicals on the lives of patients with severe asthma. As exploratory objectives this study addresses which aspects of treatment are considered important by patients, the way patients see their own role in the healthcare process, and how these findings may be used to improve patient monitoring and care. As such, in this qualitative study we aim to explore the way severe asthma patients experience their disease and its treatment.

1.1 Severe asthma diagnosis

In the last 15 years, the diagnosis of 'severe asthma' has evolved, with clinical guidelines published in 2014 formalizing the definition. This universally accepted definition of severe asthma is: *'asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy.* (Chung et al 2014, p. 344). Labelling asthma as severe includes treating comorbidities, dealing with poor adherence and incorrect inhaler technique. Common symptoms of severe asthma are shortness of breath (with and without exertion), coughing, wheezing, chest tightness, nocturnal symptoms, lack of energy and fatigue. These complaints have a major impact on the quality of life of patients and may cause stress, anxiety and depression (Porsbjerg & Menzies-Gow, 2017). About 5 % of the total asthma population suffers from severe asthma but this relatively small subgroup uses about 60% of the resources for treatment mainly due to their high use of medication (Muhrer, 2018). Patients with severe asthma have frequent exacerbations, are frequently hospitalized and have higher morbidity rates. Moreover, severe asthma appears to have a strong impact on the everyday lives of patients – most patients are unable to work and lose contact with family and friends because of their disease (Eassey et al., 2018).

Severe asthma is thus a specific and relatively rare form of asthma that is very difficult to control (control is mainly determined using the standardized Asthma Control Test or Assessment of GINA criteria using other methods). The diagnosis is however not a straightforward one, in fact severe asthma is said to be misdiagnosed in as many as 30% to 50% of cases (Muhrer, 2018), often because of comparable symptoms to COPD (Holgate & Polosa, 2006). Moreover, it is increasingly recognized that asthma is a heterogeneous disease consisting of different phenotypes (cf Heaney & Robinson, 2005; Holgate & Polosa, 2006). One of the hallmark pathological features of asthma consists of airway inflammation. Especially in severe asthma, airway inflammation is heterogeneous; allergic versus non-allergic, eosinophilic or non-eosinophilic asthma - differences relating to the types of inflammatory mediators (interleukins) involved. These insights are currently extensively investigated for their clinical relevance. Through the identification of non-invasive biomarkers more tailored treatment regimens could be developed.

For the purposes of this research, the focus is on the eosinophilic phenotype of asthma as biologicals mostly target this type of inflammation. Patients suffering from this type of asthma, about 50% of the severe asthma population (Muhrer, 2018), show a relative high number of eosinophils in their blood and sputum, and can have both allergic and non-allergic asthma. Eosinophilic asthma is relatively OCS resistant and is more prevalent amongst adults than children. The exact causes of the relative high presence of eosinophils, just as the broader pathophysiology of severe asthma is rather complex and as of yet not completely understood.

1.2 Biologicals

From the early 2000s specific medicines for asthma called 'biologicals' have emerged. These are add-on treatments such as omalizumab (Xolair®, 2003, IgE), mepolizumab (Nucala®)/reslizumab (Cinquero®) (2016, IL-5), benralizumab (Fasenra®, 2016/2017, IL-5R), and most recently dupilumab (Dupixtent®, 2019, IL4R). These biological medicines, monoclonal antibodies, are created by bacteria, fungi or cells, and are meant to directly influence the immune system by blocking a specific messenger protein, interleukin, that is involved in inflammation processes. IL-5 biologicals reduce the inflammatory process through a reduction of the eosinophil count. Biologicals are only useful for about 50% of asthma-patients, dependent on the type of inflammation (and which interleukins are involved; biologicals work on IL-4, 5 and 13). For patients with severe asthma the addition of biologicals to their treatment has proven to be effective in order to regain control over the disease (Busse, 2018), and clinical trials show biologicals having a '*relatively favourable safety profile*' (Patel et al., 2018, p. 747, cf Bleecker et al., 2016, Finn et al., 2003).

In this research we discuss biologicals broadly, but in our data-collection focus more specifically on a recently developed biological, benralizumab. Benralizumab is administered using a syringe, once every 8 weeks, with a loading dose in week 4, about 8-6x times a year – a much smaller frequency than the daily medication patients with severe asthma are accustomed to. Tests by amongst other the pharmaceutical company, show it to be rather successful add-on treatment; 74% of patients report no exacerbations of severe asthma in their second year of taking it[1]. Overall, biologicals' greatest clinical benefit lies in reducing severe asthma exacerbations, with modest effects on day-to-day symptoms and quality of life (Chung et al.,2014), thus diminishing the need for the use of oral corticosteroids, prednisone, of which side-effects are relatively strong both physically (osteoporosis, cataract, blood pressure drops) and mentally (anxiety, irritability, depression).

The use of biologicals also has some known downsides, including the high costs. The list price of benralizumab (Fasenra®) is $4,895.74 per 30 mg/mL (one dose/pre-filled syringe, March 2019, US price,

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[1] See: https://www.astrazeneca.com/media-centre/press-releases/2018/fasenra-shows-consistent-safety-and-sustained-efficacy-in-long-term-phase-iii-bora-trial-in-severe-eosinophilic-asthma-18092018.html

price differs per country[2]). Due these relative high costs it is argued that 'this medication should be reserved for patients for whom they yield a therapeutic and pharmacoeconomic advantage' (Patel et al., 2018). Moreover, it is not yet known if patients using biologicals successfully have to continue this very long-term (life), and there is a distinct lack of information on long-term effects of biologicals. Also, biologicals do not exhaustively deal with all complexities of severe asthma as they have no direct, structural effect on the remodelling of airways (Van Nederveen-Bendien, 2019). Finally, little research has been published that addresses patients' living with severe asthma, and to the best of our knowledge no interpretive research has been executed that explores the use of biologicals for this group of patients. Such an exploration seems relevant to provide the necessary lived context to existing technical pharma-economical and epidemiological research on the use of biologicals for severe asthma.

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[2] See: https://www.fasenra.com/cost-assistance.html

2 Research Design

2.1 Qualitative study design

Our exploratory research involved three steps: a targeted literature review of available literature, an analysis of patient experience stories and an interview-study with a life-history approach. We will now explain each of these three steps in detail.

2.1.1 A review of the scientific literature

The research started with a literature review of international academic publications on patient experiences in their daily lives with severe asthma and use of biologicals. We opted for a targeted review instead of a systematic review because we expected a rather limited amount of relevant publications to be available because of the recent use of biologicals for severe asthma – hence also the overall explorative design of this study. Moreover, a systematic review would have been superfluous given de very recent systematic review done by Eassey et al. 2018 on exactly this topic. These authors only note five relevant publications, none of which systematically detail patients' experiences with the use of biologicals for severe asthma.

For the targeted review we used two search strategies: snowballing through key publications, and a more systematic search using literature databases. Snowballing, i.e. using the reference list of a paper or the citations to the paper to identify additional papers, was useful to identify 7 publications directly relevant to the research question ('key'), and to construct search terms for the next step. These 7 publications all directly address the patient experience of severe asthma. From these 7 publications we constructed several search terms (severe asthma, biological, benralizumab, patient, patient perspective, quality of life, care, everyday life) that we employed in different combinations and to different effects in our search of databases – the results of which are available upon request. For a systematic review we would include databases such as Embase, PubMed/MEDLINE (including Epub), Web of Science and Google Scholar, as this combination usually leads to recall levels above 95% (Bramer et al., 2017). Since such recall is not our goal, we required a more social scientific focus in our search, we have opted to exclude Embase and PubMed because of their biomedical and clinical focus and instead focused on Web of Science and Google Scholar (1975 to current) – also because in this way we would still observe the most important biomedical and technical publications. As a safeguard we did double-check through PubMed.

In all, including the snowball strategy, we identified 29 relevant publications. We included 14 publications that dealt with severe asthma and biologicals, in particular benralizumab. These publications are more biomedical and clinical in nature and say relatively little to nothing about patient experiences. We included 3 publications that addressed broader but relevant issues on living with asthma, such as a paper detailing the development and validation of the Asthma Life Impact Scale (Meads et al. 2010). Most importantly we included 12 publications that focus on the patient experience of severe asthma, both survey and interview-based studies. In our analysis we focused on these publications, firstly scanning abstracts to discern relevant information, secondly close reading their content in order to summarize their main findings. While these publications are valuable to give insights into how patients experience living with severe asthma, as expected these say little about patient experiences of using biologicals.

2.1.2 An analysis of patient experience stories

Parallel to the literature review we have explored existing narratives written by patients in ego-documents, i.e. stories about patients' experiences as written and published by patients themselves in books or blogs.

To select these ego-documents we made use of the existing collection of patient narratives (books, blogs, etc.) at the library of the Erasmus University Rotterdam[3]. From this collection we were able, using the library's index and expertise of the manager of the collection, to select 18 relevant publications in an initial selection. We selected publications solely on them being written by adults and being about living with asthma. From these 18 publications we maintained 7 in the analysis after a first reading of the material, focusing specifically on severe asthma – none of the publications involved the use of biologicals. The 7 ego-documents, all written in Dutch, detail the authors' experiences in and outside of healthcare with severe asthma, sometimes in surprising prose (e.g. Vissers, 2006 uses a fairy-tale style narrative to share his experiences). Through our interview-study (see below) we encountered two more relevant and recent publications from the Dutch Davos Foundation (*Vereniging Nederland-Davos*) and included these in our analysis as well, resulting in 9 publications. After the initial read of the material through which we became familiar with the material, the analysis aimed to identify relevant chapters and passages in order to distinguish themes in how authors give meaning to the impact of severe asthma and care on their everyday lives. Again, similar as to the literature review, in our analysis we find detailed information on living with severe asthma, but little to no information about living with biologicals.

2.1.3 Interviews with patients with severe asthma

Building on the insights we gained in the previous two steps of this research, in a final step we interviewed 10 patients and 2 healthcare professionals in the Netherlands in the fall of 2019 in order to explore patients' everyday lives with severe asthma and the use of biologicals. The patient interviews were approached as "life-histories" in which we gave patients the opportunity to share their own experiences without over-structuring them. In these open-ended interviews respondents had much control over what information they wanted to share with the researcher. The researcher used open-ended questions to elicit spontaneous discussion of patient experience. These prompts focused on a few central themes that we developed from the findings in step 1 and step 2. These themes (such as 'receiving the diagnosis', 'experiences of care', or 'using benralizumab') were combined in a short topic-guide (in Dutch, available upon request). Rather than structuring the interview and the questions asked, this topic-guide served as a check to ensure all relevant themes were addressed. This approach enabled us in our aim to seek diversity in patients' narratives on daily life with severe asthma and the impact of biologicals.

We took patients using benralizumab as our focus and included patients who are currently using benralizumab and who have (recently) stopped doing so. In order to develop a broader understanding of the themes related to the therapeutic area as a whole, we also included one patient who had no experience with benralizumab and is currently using a different biological, and one patient who had no experience with biologicals and was not diagnosed with severe eosinophilic asthma. The concrete inclusion criteria we used for the patients consisted of the following items:

- Adult (≥18 years).
- Severe asthma diagnosis.
- Current or recent treatment with benralizumab. Treatment has had to be started before the start of the study in August 2019 as to ensure this study is not used as, or perceived as, a seeding trial, and to avoid incentivising clinicians or patients to prescribe or use benralizumab or a different biological.
- Idem as above but, for 2 patients, past or current treatment with a biological that is not benralizumab, and who have had no experience with benralizumab.
- Able to participate in a 60-90-minute interview to discuss their severe asthma and experience with biologicals
- Written informed consent.
- Able to express him/herself in Dutch.

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[3] See: www.patientervaringsverhalen.nl

Respondents were selected from non-academic hospitals, contact to which was established with help from AstraZeneca. Recruitment and selection were however done by way of the interaction between the physicians who informed patients of the study and the primary researcher following up on initial consent to participate with detailed information, a written patient information folder and consent form, and an appointment for an interview. Interviews were, in all cases except for one (P008), executed in the homes of the respondents throughout the Netherlands. The shortest patient interview lasted 43 minutes (P009) whereas the longest was 86 minutes (P003), on average interviews lasted 56 minutes. All respondents consented to having their interview audio recorded. These recordings were subsequently transcribed verbatim to enable detailed analysis.

See Table 1 for details on the respondents but to summarize: our sample consist of more women (7) than men (3), more respondents have an intermediate level of education (6/10), the youngest respondent is born in 1972 (48), the oldest in 1951 (69), most respondents experience relative success with using benralizumab (6/10), and two respondents have no experience with benralizumab at all. Importantly, for most of our respondents, other diseases are also involved in their everyday experiences of health and illness. One respondent (P008) survived cancer three times, another survived breast cancer (P001), and yet another struggles with iron accumulation in his blood (P007). The patient interviews were supplemented with two interviews with specialised health care personnel (respiratory nurse, pulmonologist). These interviews helped us to contextualize the patient interviews.

Table 1: Overview of respondents

Respondent	Gender	Year of birth	Education (Dutch level)	Biologicals (effect*)	Remarks
P001	Woman	1965	Intermediate (MBO)	benralizumab (success)	
P002	Woman	1972	Intermediate (MBO)	omalizumab (no success), benralizumab (no success)	
P003	Woman	1963	Intermediate (MBO)	mepolizumab (no success), benralizumab (success becoming less)	
P004	Man	1954	High (HBO)	dupilumab (success)	Married to P005
P005	Woman	1956	High (HBO)	none (allergic severe asthma)	Married to P004
P006	Woman	1968	High (PhD)	benralizumab (success)	
P007	Man	1970	High (HBO)	omalizumab (no success), benralizumab (success)	
P008	Woman	1968	Intermediate (MBO)	benralizumab (success)	
P009	Woman	1952	Intermediate (MBO)	benralizumab (success)	
P010	Man	1951	Low (Basisonderwijs)	benralizumab (succes)	Interview with wife
A001	Pulmonologist				
A002	Pulmonary nurse-specialist				

* Effect as mentioned by respondent during interview.

Similar as to the analysis of the ego-documents, the interviews were analysed through a close reading and iterative thematic coding of the material. The initial coding scheme (available upon request) used was based on the topic guide. As such, the analysis focused on thematically categorizing how respondents give meaning to the impact of severe asthma on their lives, the impact of care and patients' reflection on their own role in the process of care. Our empirical material – i.e. these transcribed interviews and selection of ego-documents – does not allow for empirically generalizable comparisons of, or conclusions about, the workings, effectivity and/or safety of the biologicals or any other treatment for severe asthma – nor is this in any way part of the aims of this research or our analysis.

2.2 Procedural and ethical considerations

This study did not require approval of a medical ethical committee as was confirmed by the advice of the METC committee (MEC-U, W19.113/NWMO 19.05.023), through Dutch Clinical Trial Foundation. However, the study is performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies. Part of such considerations is that fact that the primary researcher was trained in identifying and reporting serious adverse events and product complaints if and when these were observed.

Patient ego-documents and scientific literature were readily available as books or online documents and were studied as such. For the interview data explicit effort was taken to ensure respondents were aware of any potential risks and benefits of participating in this study. Respondents were made aware twice, through a detailed patient information form (in Dutch, available at request) and verbally before the start of the interview, of the details of the study (purpose, nature, risk and benefit) and of the voluntary nature of their participation. It was stressed to respondents that consent could always be withdrawn without providing any reason for it, and ample space was provided for respondents to ask questions or voice their concerns about the study. Respondents' consent to participate has been confirmed verbally and in writing by signing the informed consent form. These signed forms are stored at the Erasmus University Rotterdam. Respondents and the physicians who aided in the recruitment have not received financial compensation for their participation in the study. Data was made anonymous upon transcription. Respondents were given an identifier code (see Table 1), the key between this code and personal information (such as name, contact details) of respondents is encrypted and available only to the primary researchers. The anonymous data is stored, and archived upon formal completion of the study, on a server of the Erasmus University Rotterdam, as such maintaining confidentiality.

This study has been executed by researchers from the Erasmus School of Health Policy & Management through an addendum to the existing agreement between the institute of Medical Technology Assessment (iMTA) and AstraZeneca BV in The Hague (addendum D3250R0063, 22-05-2019). This agreement ensures amongst other the independence of the researchers in the design, execution and reporting of the results of this study.

3 Results

3.1 Results literature review

Before we set out to discuss the empirical results of our study, here we summarize the main findings from our review of existing literature on the patient experience of living with severe asthma and the use of biologicals.

The literature review was aided much by a recent systematic literature review that concludes that little is known and published about this *'small and often invisible group'* (Vereniging Nederland-Davos, 2019, p. 3) of patients living with severe asthma, and even less is known about how these patients consider the use and effects of biologicals (Eassey et al., 2018). The review finds how the extant literature on these topics generally emphasize clinical instead of personal issues. Moreover, on biologicals, the literature makes clear that there is a:

> *'… paucity of literature reporting patients' experiences of add-on biologic treatments such as omalizumab, mepolizumab, reslizumab and benralizumab for severe asthma. Their greatest clinical benefit is in reducing severe exacerbations, with more modest effects on day-to-day symptoms and quality of life […]. This divergence points to the need for future qualitative research to explore the impact of these treatments on the overall lived experience of patients with severe asthma'* (Eassey et al., 2018, p. 318).

Before taking up this rather explicit call for research, below we consider some more general aspects of living with severe asthma that do emerge from existing scientific literature and that result from our review. We do so by making a distinction between the *burden of disease* and the *burden of treatment* (May et al., 2014). The burden of disease is generally the burden of symptoms that patients experience, whereas the burden of treatment refers to the experience of patients of *'new and growing demands to organize and co-ordinate their own care, to comply with complex treatment and self-monitoring regimes, and to meet a whole range of expectations of personal motivation, expertise and self-care'* (May et al., 2014, p. 2). The burden of treatment thus refers to the engagement of patients with their own (chronic) conditions that cannot be cured but rather must be managed.

3.1.1 Burden of disease

The literature shows the large impact of severe asthma on patients' everyday life; the onset of severe asthma is being described as a *'major kind of disruptive experience'* (May et al., 2014, p. 7). The burden of disease for severe asthma means that patients find themselves continually short of breath, fatigued and at risk for fearful exacerbations, unable to breath, and in need of regular medication. Besides physical distress, patients report to live in fear: '[the 2007] *severe asthma survey reported that one in five patients lived in fear that their next attack would be their last*' (Eassey et al., 2018, p. 317). As such, patients with increased symptom burden are found to be at higher risk for developing depression (Yonas et al., 2013).

The burden of disease of severe asthma is in many ways similar to patients' reports on living with other chronic illnesses, e.g. in the reported feelings of dependency, uncertainties around long-term medication use and issues with adherence. Severe asthma is particularly said to be different to many other chronic illnesses in its 'invisibility' to outsiders - others do not readily notice the manifestation nor recognize the severity of severe asthma - and in the unpredictability of potentially life-threatening exacerbations/flares of severe asthma (Eassey et al., 2018, p. 317).

Severe asthma is found to have a strong impact on patients' social and societal participation. A survey finds that 27% of patients reported to have lost contact with family and friends, and 66% are not able to work full-time (Eassey et al., 2018). As such, severe asthma patients and their families also face economical burdens. Franco et al (2009, p. 478) show how '*family costs of severe asthma consumed over one-fourth of the family income of the underprivileged population in a middle-income country* [Brazil]', stressing the economic consequences and (potential) inequalities in the experience of this burden. Particularly troublesome for patients in social interaction is the 'stigma' of asthma in that people tend to consider asthma as relatively a mild and easily treatable condition. Severe asthma as such often appears rather misunderstood or not acknowledged in its severity (Foster et al., 2017). On a practical level this can lead to workplace conflicts (Apps et al., 2019), but research also reports how interviewees felt '*misunderstood and alone in their experience of breathlessness and frightening exacerbations; practical and emotional support needs were often lacking and the emotional distress of severe asthma was amplified in those with little support*' (Foster et al., 2017, p. 1). Quite clearly the existing literature is emphasizing that the burden of disease of severe asthma moves beyond the boundaries of the experience of the symptoms (shortness of breath, coughing, pain in the lungs, fatigue, etc.) to that of troubles in (intimate) social interaction and patients' societal participation.

3.1.2 Burden of treatment

The treatment of severe asthma consists of medical and non-medical practices. General goals of treatment are '*to reduce asthma severity by controlling symptoms, preventing exacerbations by lowering risks, avoiding exposure to allergic,* [and non-allergic triggers such as] *physical, and chemical triggers, and by developing a medication regimen that minimizes adverse side-effects while also matching patients' preferences and goals*.' (Muhrer, 2018, p. 520-521). For patients this means living with regular use of medication with (risks of) side-effects and (large lifestyle changes on issues such as weight management, stop smoking and regular exercise, and avoiding triggers at work, at home (pets), and in everyday social life. Patients thus often must consider their disease in planning, routines and in dealing with triggers. Therefore, the burden of severe asthma treatment is said to be relatively high, especially regarding the burden resulting from the prolonged and intense use of oral corticosteroids (OCS) (Hyland, 2015; Foster et al., 2017), side effects of which include amongst other depression, irritability, sleep, hunger, weight-gain, skin, gastric, pain, disease anxiety, and medication anxiety (Hyland, 2015) (cf Eassey et al., 2018; Apps et al., 2019).

With severe asthma being misdiagnosed in as many as 30% to 50% of cases (Muhrer, 2018), patients generally have (had) a relatively large amount of interactions with healthcare professionals. The burden of treatment also involves these interactions, also called health care utilization, like visits to, and repeated stays in hospitals. In addition and in line with a general trend, several authors call for patient empowerment and self-management (Eassey et al., 2019). As this shifts responsibilities to patients, this can increase the burden of treatment as experienced by patients. This depends on the support they receive from healthcare professionals though. Menzies-Gow et al. (2018) call in a recent charter, amongst other, for proper support for patients in understanding severe asthma, to not be reliant on OCS and to have consistent access to quality care.

However, access to comprehensible information is not self-evident (Ross et al., 2010). Asthma information was often viewed as '*inadequate due to lack of scope and or plain language*' – most valued sources of information where acquired through the specialist and the '*pulmonary rehabilitation program*' (idem, p. 330). This is not without consequence; low health literacy is associated with poor outcomes in moderate to severe asthma, in particular through achieving more or less control on the asthma (Apter et al., 2013). In case of 'epistemic tensions' on asthma, researchers note how patients respond in two ways; either by incorporating expert knowledge or by resisting and challenging expert knowledge – both leading to feelings of frustration and uncertainty (Haw, Cunningham & O'Doherty, 2018) – adding to the burden of treatment.

The literature is very scarce on data considering the burden of treatment with biologicals. Biologicals are meant to serve as add-on medication, a product to be used as a last resort. Biologicals such as benralizumab only need to be administered once in 1 or 2 months – much less frequent than usual asthma medication. However, we find that '*some felt inconvenienced by attending regular appointments for injectable biologicals'* (Foster et al., 2017, p. 5). Biologicals are also mentioned to offer '*hope for preventing their asthma worsening in old age*' (Foster et al., 2017, p. 8). In this way biologicals, if they are effective for a patient, seem to lighten the burden of treatment by moderating the inflammation and risk of exacerbations. This diminishes the need for OCS, and reduces its side-effects, and in turn diminishes frequent interactions with healthcare professionals and appears to offer hope for the future.

3.1.3 Balancing burden of disease and burden of treatment

For patients with severe asthma both the 'burden of disease' and 'burden of treatment' seem to be high, requiring a balancing act in everyday life. The literature shows that such a balance, if at all found and maintained, involves quite some work – for instance in interaction with clinicians, or in avoiding triggers at home – tinkering with doctor's advice:

> *'I was told that I was to not have [birds] because they carry bird fancier's disease. Yeah but his cage gets kept clean and he runs the house. So, what my specialist doesn't know won't hurt me'* (Eassey et al., 2019, p. 5).

This balancing work, in the case of the quote between doctors' advice and potential triggers, can be done in a more positive way – through acquiring self-management skills, or through more negative strategies (e.g. over-vigilant monitoring of symptoms) that do no help in reducing either of the burdens (cf Foster et al., 2017). The literature points out that the main impetus for patients to balance the burden of disease and treatment is to enhance *autonomy* in everyday life, and *control* over their disease. An important part of this seems to be a certain ambivalence to medication, and somewhat of a disconnect between the clinical disease-managed based and patients' everyday lived realities (Eassey et al., 2018). For instance, it is reported that patients understand their asthma to be 'in control' when it is not getting any worse, whereas the more formal definition, and standard Asthma Control Test criteria emphasize that control means symptoms are being prevented (Bidad et al., 2018):

> *'A large discrepancy was observed between the proportion of patients who perceived their asthma to be well controlled (42%) and the proportion of patients who reported to be well controlled as per the Global Initiative for Asthma (GINA) assessment (6%). Although most patients perceived their asthma to be controlled, many experienced frequent symptoms that affected their daily lives*' (Katsaounou et al., 2018, p. 1).

This shows that there is no consensus on how that balancing act between disease and treatment should be done, or when it is achieved. However, it is also clear that for some patients severe asthma is just beyond control, and patients also hide their symptoms, for instance at work:

> *'For some participants, perceptions of asthma by others posed challenges in the workplace. Participants found themselves hiding symptoms or felt concerned that a regular cough was irritating to coworkers'* (Apps et al., 2019, p. 2).

Apps et al (2019, p. 2) also note that '*adherence to self-management plans is poor in the context of everyday life*'. In this way, finding the balance between disease and treatment burdens is more than 'self-management' of disease (Eassey et al., 2019) as research finds it to be strongly connected to patients' desire to live an 'unconstrained life', and to 'preserve self-identity'. In the literature we found that treatment with biologicals for severe asthma, if resulting in a good clinical response, appear to have a significant positive impact on both the burden of disease (less symptoms, less risk of severe exacerbations) and on the burden of treatment (in particular because less need for OCS avoiding its side-effects) – although some indication is given of inconvenience experienced by patients because of the regular injections.

3.2 Empirical results

In this paragraph we detail our empirical findings relating to the experiences of the burden of disease and the burden of treatment of severe asthma as our respondents have shared with us in the interviews and through their ego-documents. We start by discussing the burdens of disease and treatment and end by focusing on how repondents narrate their experience of biologicals.

3.2.1 Burden of disease: dealing with symptoms and avoiding triggers

Dealing with symptoms

In general, our empirical results on patients' experiences of the burden of disease aligns well with the existing literature as discussed above; respondents appear to experience the overall burden of disease of severe asthma as a heavy weight. For most respondents, this starts in particular with having trouble breathing:

> *'… like a fish on dry land, yes, that's how I feel. Hoping for air, everything in my whole body tries to just catch this tiny little breath of air'* (Talsma, 2015, p. 206).[4]

Such breathlessness is experienced under high tension – as the quote shows, in the experience of the patient, the whole body is working, struggling to catch enough air. This effort itself is experienced as draining energy: *'It is hard work to get the oxygen in'* (Kuipers, 2013). Breathlessness and other symptoms, such as coughing, can reach such severity and can become so common also to others, that respondents are being identified with it:

> *'Also, in my work they said: 'I do not know what that lady is called', but that is the lady who always coughs, so. Yes, that's what they said of me, I am known as 'that lady who coughs so much'* (Respondent P009).

Breathlessness, being short of breath, and coughing are generally a continuous experience for patients, but severe asthma can flare in intense exacerbations whose occurrence is difficult if not to control for the respondents. Except for respondent P004 all respondents have experienced these sudden exacerbations of their severe asthma, and respondents who have, describe it is an intense experience:

> *'… so I had two surgeries done to my nose* [for nasal polyps]*, but they didn't help much. I had little trouble in the beginning, but after a certain point I just started coughing, and I got blackouts, I was knocked-out twice. I was gone'* (Respondent P001).

To blackout is described by respondents as a very fearful experience, in case of P001 for her daughters in particular. These moments often lead to emergency admittance in hospitals, and prolonged stays to recover:

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[4] All quotes in this chapter are translated from Dutch to English and edited for readability by the first author.

> *'R: Well, I went to the GP again for a prednisone cure, and I... I could hardly talk to the doctor.*
> *I: Were you that short of breath?*
> *R: Yes, and then there was a replacement-GP and she was so shocked, and [...] she [did] some tests, she did, and said: 'It is not good, I want you to go to the emergency room', or whatever, to the [name regional hospital] because they could not take me in the [academic hospital]. I sat there all evening and finally they took me in, and I got a prednisone infusion'* (P006).

Respondents often and rather casually talk about having to be rushed to emergency care or are being hospitalized for a longer duration as a consequence of the lack of control of their asthma. Severe exacerbations, prolonged extreme breathlessness requires respondents to be sometimes hospitalized for weeks, and for repeated times – some respondents and authors having been hospitalized for more than 15 times. This is experienced as very frustrating, and the sheer frequency appears to influence care seeking:

> *'I just want to be normal, just live ... I refuse any admittance because I just don't want to anymore ... don't want to let my health ruin another year, I want to stop worrying about my health!* (Talsma, 2015, p. 67).

Talsma clearly illustrates the frustration experienced by patients in being halted in life, in having little to no control in everyday life, perhaps taking back such control through refusing admittance. Such frustration is heightened through respondents' respiratory distress, lack of energy, and the volatility of exacerbations - it is difficult for respondents to predict when an exacerbation will occur, or when fatigue is too severe.

Managing triggers and social life

With symptoms being unpredictable and energy-levels low, respondents share many examples of the importance of controlling triggers of these symptoms in order to avoid exacerbations. The management of these triggers appears to have strong consequences for respondents' social life and societal participation. All respondents have examples of dealing with triggers, or of failed attempts to do so: P005 does not enter a lift if it smells of perfume. P007 started to do less dusty things at the children's farm, changing his job, also to keep his disease hidden. P008 avoids smoking friends, and thus loses a large part of his social life. Sometimes triggers cannot be avoided; P009 has worked for a long time in home care in the time that people 'still just smoked' inside their houses. P008 had to climb eight stairs from her flat to her house - there is no elevator, and it could take an hour before she was upstairs because of all the breaks she needed to catch her breath:

> *R: If you are not breathing it becomes really difficult,* [...] *I was really watching for another house, because I thought I can stay in that apartment for a while, but then I can't go upstairs much longer...*
> *I: Is there no elevator in it?*
> *R: No, and there are sixteen steps, eight this way and eight the other. And if you had trouble with the first eight then you first had to rest for a while and then you could take the other eight and then you were finally inside' (*P008).

Having to move houses seems a rather strong consequence, but many respondents share emotional stories, when prompted, about the loss of friends, acquaintances and family because of having to deal with the triggers affecting their symptoms. Some respondents still had regular paid employment at the time of the interview (P004, P006, P007), or have continued to work until retirement, but most were not able to do so. Generally, respondents mention to struggle with people's incomprehension of the severity of their asthma. Even at meetings of the Dutch Lung Foundation (*Longpunt*), people wear perfumes that cause problems for respondent P005. As a result of this experienced incomprehension respondents mention to not go on broadcasting their illness. P007 is striking in the determination with which he states not to be open about his disease, he does not want to appear sick and weak:

> '[I had] *a brace once and everyone found me pathetic, everyone who saw me then knew that I was not well. But when the brace went off* [...] *I was no longer pathetic, at once I could do everything again. I still couldn't do anything, I had the same pain I had the day before and at some point, just... People are hard, the only one being hurt is me, because people say: '*[P007] *is the klutz of the neighborhood, we will ask someone else to help'* [...] *so I just said nothing anymore, so I am involved and my life remained intact. And when something was impossible* [for me to do], *I would make a joke and let someone else do it, but I was there, and I was part of the group that was working'* (P007).

In this quote, the visibility of the brace P007 once had contrasts strongly with the invisibility of his severe asthma, the severity and existence of which he has chosen to keep silent in order to keep on being 'part of the group', in order for his everyday life to remain 'intact'. He mentions to be able to avoid the most intense triggers by making a joke, an example of social coping, but this is not the answer for all respondents. Respondents appear not to allow themselves to be guided solely by their diagnosis of severe asthma. And there is, needless to say, always more going on in respondent's everyday lives than just this disease; in addition to being sick herself, P008 is also a daily caregiver of her mother-in-law of 90 years. And P010 would rather talk about the weekly visits he makes with his wife to the campsite than about a disease that he actually thinks he does not have.

3.2.2 Burden of treatment: finding a diagnosis and managing treatment

Just as with the burden of disease, our results on the burden of treatment are close to findings in existing literature. Whereas respondents work to regain control and autonomy in their everyday lives, treatment for severe asthma often is not effective enough to do so. We also find evidence of patients' ambivalence to medication, and of disconnections between the clinical and patients' everyday lived realities when patients start to 'doctor' themselves.

Finding a diagnosis

To get specific treatment one first must be diagnosed. Respondents (except for P005 and P010) share in their interviews how they have shown signs of asthma throughout their lives, but only recently having received the diagnosis of 'severe eosinophilic asthma'. Biologicals can play a part in this diagnostic process for patients:

> *'I have always accepted that I had asthma, okay, and I am very happy that now in fact it has the stamp of: this is it and nothing else. You can say that the syringe* [benralizumab] *is effective for me, but first see if it really works for me* [...] *after two injections I had something like, this oh yes this is it, finally'* (P001).

Respondent P001 expresses to be 'very happy' to now know for sure the kind of asthma she has, because of benralizumab being effective. This moment, however, is the final step in a long process that for some respondents has taken decades, has involved many different professionals and many different kinds of treatment – for most of our respondents culminating in getting benralizumab. Respondents relate often to the way they have been treated in regional hospitals and primary care for years. They share stories that generally appear to consist of patients and healthcare professionals 'muddling through' inflammations and exacerbations through prednisone, anti-biotics, etc. In this way, for most respondents, such as P003, their disease and life course are intrinsically woven together:

> *'Well, it was during puberty, I think,* [...] *I got stuffier often, just short of breath* [benauwd] *just from one minute to the next, or even shorter that I was really out of breath and yes in the beginning my parents, bit old-fashioned, that was the doctor that was a very important person like the pastor... '* (P003).

With her disease not being recognized as impotent enough to visit the 'very important' GP, a person not to bothered with a 'stuffy' girl, throughout her adolescence and subsequent marriage she suffered symptoms without any concrete assistance. As such, her experience of everyday life became immersed with suffering, and our interview turned into an emotional conversation. Other respondents also talk about being misdiagnosed (P007 – focus on upper airways, P008 – COPD) and in hindsight unnecessary surgical procedures (P001). These seem to be extreme cases, but almost all respondents recount such a process that lasted until a correct referral to a severe asthma specialist had happened and the correct diagnosis followed. This referral to the specialist in the accounts of our respondents only happened at moments when respondents' health situation had deteriorated very much.

Not everyone with this diagnosis agrees with it or values it as highly as Respondent P001 does in the quote above. Respondent P010, for instance, has only very recently and rather lightly been suffering from symptoms, making him explicitly doubt his diagnosis:

> *'I: Yes* [generally people tell us] *it started very early in my life, and a lot happens, and I always had trouble with it, but with you, that is not the case at all?*
> *R: No, that's why… I have that injection, now for the fifth time, so I don't know if it helps. I don't suffer from asthma, what is asthma? I recently watched something on TV, people who have asthma who can't go outside when someone has the fireplace going. I have had no problems with that.'* (P010).

Not severely suffering from symptoms, combined with the late onset for him, does not match with his picture of asthma as those 'who can't go outside when someone has the fireplace going', leading P010 to explicitly doubt his diagnosis. And for P004 the severe asthma diagnosis is much less relevant than the eczema he suffers from as well. Interestingly, only respondent P006 argues that eosinophilic asthma is actually not really asthma at all, despite having received this diagnosis:

> *'…. the pulmonologist actually told me after a short conversation; 'it seems like you have eosinophilic asthma, that is actually not an asthma, that is another form, and that is actually a prednisone-independent asthma'. Then, I went there to look up articles and it corresponded exactly with what I had* […] *she wanted to know my number of eosinophils in the blood and that was much too high'* (P006).

Respondent P006 argues that her asthma originates from a specific work-related event. She is, however, a rather specific respondent in that she is trained as biologist, highly knowledgeable and able to navigate relevant academic literature easily.

Trusting professionals

Despite the relatively long trajectories respondents share in the interviews, and account for in the ego-documents, in general respondents appear to have a strong sense of trust in healthcare professionals, especially in the professionals who are currently treating them. Regular check-ups, controls and advice are deemed important – even though such tests are strenuous themselves: '… *but first we blow the big torture test called lung function'* (Talsma 2015, p. 42). Levels of trust seems to vary based on respondents' amount of health cultural capital or 'health literacy'; respondents who appear more able and willing to (re)search for information themselves or to pave their own way in healthcare, appear often also critical of care professionals. For example, P007 is very critical of poor communication between the ENT doctor and pulmonologist:

> *'but* [my] *lower airways were difficult, and nobody was interested. And I always wondered why there was so little communication between the pulmonologist and ENT doctor, but I still notice that communication is not always going well'* (P007).

Issues in the communication between specialists and to patients can be experienced by respondents as increasing the burden of treatment, i.e. increasing the difficulties in creating control and autonomy in patients' everyday lives. However, supportive specialists, that patients trust, might conversely alleviate such burdens.

Managing treatment

For our respondents, and the authors of the ego-documents, the burden of treatment consists of quite a few different aspects. In their accounts, the regular use of many different kinds of medication (inhalers, etc) is especially prominent:

> *'I understand that at the moment I have no other choice than to take medication regularly. But somewhere I keep my fear that even the best doctor in the world cannot completely take away. Because the scientific experience of the doctor is a reality and the medicines in my body are another. I continue to struggle with that'* (Niklaus, 1994, p. 17).

The struggle Niklaus notes in his book about 25 years ago is recounted quite similarly in other ego-documents (e.g. '*My mind and body are regularly having a fight*' (Vereniging Nederland-Davos, 2019, p. 24)), but also in our interviews. Respondents talk about always having to maintain, and have readily available, a stock of medication, and share feelings of dependence. However, issues of uncertainty, unpredictability and loss of control do not dominate as much in the interviews as we would have expected based on the literature. Two possible explanations for that might be that respondents now have the balance in order – our sample is biased to respondents successfully using biologicals - or it is because of the overwhelming seriousness of severe asthma: *'being ill started to become a part of me'* (Talsma 2015, p. 30). Still, also our respondents experience only limited control in taking their medication or not, the management of this small space of control is generally dominated by ideas of adherence and control derived from evidence-based clinical guidelines instead of patients' everyday lives. Not surprisingly, some respondents, such as Niklaus above, show to have a rather ambivalent relationship to their medications and treatments, whereas others show to be more straightforwardly at ease with their medication use. Of all medication, oral corticosteroids (OCS) are mentioned most explicitly by respondents; either as something that kept them going despite all odds, or as medicine to be avoided – mainly because of the side effects of feeling bloated (*opgeblazen*). As Thomas (2013) writes after having to restart prednisone upon returning from Davos:

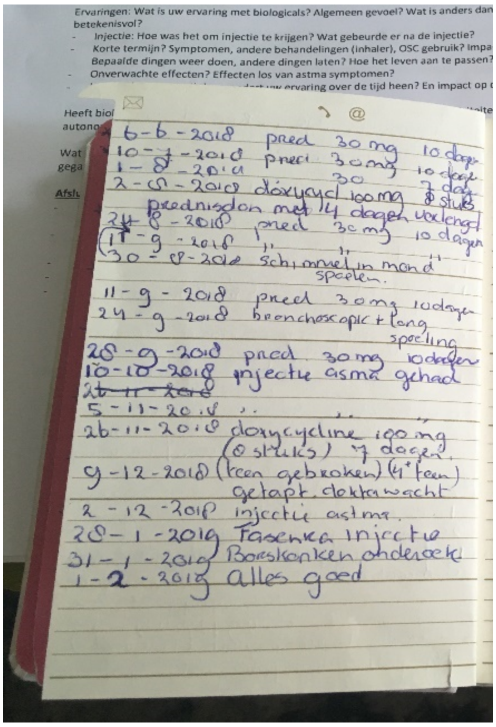
> *'I'm very disappointed, I really don't want this! But I don't really have a choice…'* (Thomas, 2013, p. 117)

Next to OCS respondents mention in particular treatment with a strong focus on self-management techniques, for example by practicing breathing and inhaler-techniques (see Figure 1 below) or creating an exacerbation plan with the nurse (A002). Respondents mention to learn such self-management techniques, linked to a more holistic perspective to patients' life, rather effectively in revalidation centres. Respondents and authors mention that pulmonary rehabilitation (e.g. high-altitude rehabilitation in Davos or in the Netherlands) are generally positive experiences, being taken out of their normal routines:

> '*I only realized how bad my asthma was, when I ended up in a negative vicious cycle last year*' (Vereniging Nederland-Davos, 2019, p. 19).

To escape negative vicious cycles of triggers, symptoms and treatment appears to work in rehabilitation centres in the Netherlands and abroad, but this is simultaneously also experienced as a very intense (though effective) step: removing oneself from existing routines in everyday life, and thus from the home, family and friends, for sometimes weeks, are part of the treatment.

Figure 1: Photographs by Respondent P008 after the interview to show which devices she uses. On the left her inhalers, on the right an exercise device.



Ervaringen: Wat is uw ervaring met biologicals? Algemeen gevoel? Wat is anders dan
betekenisvol?
- Injectie: Hoe was het om injectie te krijgen? Wat gebeurde er na de injectie?
- Korte termijn? Symptomen, andere behandelingen (inhaler), OSC gebruik? Impa
Bepaalde dingen weer doen, andere dingen laten? Hoe het leven aan te passen?
- Onverwachte effecten? Effecten los van astma symptomen?

6-6-2018 pred 30 mg 10 dagen
10-7-2018 pred 30 mg 10 dagen
1-8-2018 30 7 dag
2-8-2018 doxycycl 100mg 8 stuks
prednisolon met 4 dagen verlengd
24-8-2018 pred 30 mg 10 dagen
11-9-2018 " " "
30-8-2018 schimmel in mond "
spoelen.
11-9-2018 pred 30 mg 10 dagen
24-9-2018 bronchoscopie + long
spoeling
28-9-2018 pred 30 mg 10 dagen
10-10-2018 injectie asma gehad
~~26-11-2018~~
5-11-2018 " " "
26-11-2018 doxycycline 100 mg
(8 stuks) 7 dagen.
9-12-2018 (teen gebroken) (4e teen)
getapt. doktrawacht
2-12-2018 injectie astma.
28-1-2019 Fasenra injectie
31-1-2019 Borstkanker onderzoek
1-2-2019 alles goed

Figure 2: A journal page from Respondent P001. Clearly visible is the repetition of prednisone cures (*pred*) to the first benralizumab shot (*injectie astma)* on October 10, with the final input that now 'everything is fine' (*alles goed*). (Photo by first author during

'Doctoring' by patients

Respondents mention often to both be loyal to the treatment as provided, while at the same time giving ample examples of moments in which they have taken matters into their own hands. Respondents also often 'doctor' themselves. This is expressed, for example, in (learning to) feel your own body and predicting attacks, to such extent that respondents argue against the doctor if necessary:

> *'Yes, I had a fight with that new doctor who said: 'no I am against prednisone'. Yes, I said you can be, but I have an agreement* [with her normal GP] *I feel my own body. 'Well yes, I give you antibiotic the doctor' said, and I said: 'You can do it but I said, but in the weekend then I'll call* [my GP] *immediately, so then I got them anyway*' (P001).

Respondent P001, who has great faith in her GP, is also very critical of the new doctor, a replacement GP who, during a period of many prednisone treatments did not trust her own judgment of her body and treatment and did not want to prescribe her treatment. See also Figure 2. This new doctor, as such, made the self-management effort of this respondent more difficult. This shows how such management is very much an interaction between different actors. Interestingly, our interviews where the spouse of the patient was present as well (P004/P005 and P009) show how 'self' management is a shared instead of individualized effort. P005 seems to follow his wife in her efforts, and P001 reasons from her family, her daughters, all the time. Remarkably, in this light, is that we found very little active search for fellow sufferers. Only P002 says, about going to a revalidation centre:

> *'R: You don't have to sit in a room together, but* [...] *conversations started automatically, so that was nice. I am still in touch with* [...] *a young asthma patient I met there and who has the same symptoms as me, and who also did not benefit from the Xolair either.* [...] *We still have a lot of contact and I like that very much* [...]
> *I: What do you like best about that?*
> *R: Well for a bit, the recognition, but also the support for each other...'* (P002).

Whereas respondents thus can take matters into their own hands, doing self-management and treatment is not an individualized affair.

The use of complementary (alternative) medicine is also a part of these 'doctoring' practices to take matters in one's own hand. Many respondents mention to have at least tried such alternatives. In our respondents view this is mainly of a relatively mild homeopathic nature – for respondent P009 for instance *'Dr. Vogel is in the house'*. In the interviews we needed to prompt respondents for this rather explicitly, in existing ego-document this was more explicit, for example in one author whose asthma improved as a consequence of: *'by investigating the karmic pools of my subconscious and confronting myself with myself'* (Veelen-van de Reep, 2004).

3.2.3 Living with biologicals: cautiously embracing a last straw

The added value of our empirical study lies in particular in the experience of our respondents with using biologicals. This paragraph is only based on the interview data, seeing that the authors of ego-documents did not discuss biologicals. In all, we find how respondents narrate the use of biologicals in the context of their experiences of the burden of disease and treatment as discussed above. For the respondents for whom the biologicals work, the positive impact on the burden of disease appears to be especially high. Respondents mention how both the burden of and of treatment are lightened to a large extent, but they are generally cautious in their embrace of biologicals and in expressing hope for the future. Moreover, for some respondents biologicals prove not to be as effective as they had hoped for.

Learning about biologicals
Respondents have generally only recently learned of the existence of biologicals. They learned about the (possibility of) biologicals through their specialist, usually before they were sent to the current specialist who actually provides treatment with biologicals. These specialists provide the basic information themselves, answer questions, and share informational leaflets made by the producer of the specific biological. Respondents with high cultural capital (such as P006) also mention to have researched their condition and possible treatments themselves on Google and Pubmed. Other patients learn about the drug through the Long Fund or the media, - such as reports on the 'magic drug' from Bennie Jolink:

> *'R: ... a year before I got it Bennie Jolink* [regional celebrity folk-singer] *also got it, and yes, well, I was fan* [of him and] *I thought yes if it works that well for him, why not for me? So, I asked for it'* (P007).

P007 has been rather proactive on getting the biological, but for most respondents the topic was broached to them by their specialist. It is striking that, during the interview, respondents often have a hard time recalling the brand name (Fasenra®), active substance (benralizumab) or general category (biologicals) – 'the injection', is rather what they call the biological they are getting:

> *'R1: Well first this 20 milligrams* [of prednisone], *and then 5,* [...] *and then at a certain moment the doctor came and said: 'yes, there is a new medicine, an injection'*
> *I: And we're going to try that?*
> *R1: We'll try that'* (P010).

Three respondents have had experiences with more than one type of biologicals, two have been treated with the first available biological (from Xolair), and they appear more knowledgeable about the type of drug:

> *'… and then she said: 'well, there will be another study', if I wanted to participate in this research, there were also new drugs; the Fasenra, benralizumab, and if I wanted to participate in that study. It took 9 months, I thought, and I got 4 injections. Well it was a very intense investigation; I was pretty blowing each morning and evening and you had to keep a whole diary'* (P001).

Having learned about the biological and their possible effects, most respondents appear to be reasonably sober in their expectations with regard to medication. 'Let's wait and see' appears to be the general attitude. These emotions, hopes and expectations are also actively managed by healthcare professionals as the interview with the nurse-specialist clearly showed:

> *'Yes, the preparation is very important. That they have no high expectations, and also that if it goes wrong that it is not up to us, because it is your body has let you down and of course you have anger and frustration towards us* […] *you try through motivational conversation you try to convert that negativity into positivity is very important'* (Respondent A002).

Using biologicals
Most respondents have just recently, for a year or less, started using biologicals – benralizumab has not been available for much longer. Often respondents use these biologicals in a somewhat experimental setting. Such settings require quite some work from the respondents, especially when being part of a study: as P001 mentioned in the quote above, she has to do regular tests, keep a journal, etc. However, few respondents comments on the actual use of the biological – we have to actively prompt for it in the interviews. Respondents tend to be quite opaque about it; it is about a shot, an injection, and they have to go to the hospital every now and then. This often works fine, is not real big issue to them and, unlike inhalers, does not require extensive training, as such indication a much lower burden of treatment:

> *''The first time I got it I had to wait for two hours because you can get side effects and* […] *then you get the medicine a month later again, because it is every month, and then you just see your lung values going up. Once you see more capacity in your lungs without me having increased my medication, I think: 'hey that's funny stuff it works!' and then after 3 to 5 months, I really have not once really been stuffy* […] *so you go slowly you discover that you can do more than before'* (P007).

Waiting for some hours, having to go to the hospital on a bimonthly basis (in case of benralizumab), is for P007 and other respondents not a very large burden, especially when you see the effects as P007 does. For some respondents this monthly visit is also a comforting affair, an 'outing' (*uitje*). Everything is checked-out, it is nice to have these tests and controls, and the meetings with the specialist or nurse can be encouraging. The relatively new idea for patients to inject themselves at home is something most respondents are aware of:

> *'Soon I will have to do it at home, but then I will know how it all works. I actually don't know yet, I'll have to learn how to inject first - they will be working on that next December. Afterwards it is the idea I still visit the pulmonologist twice a year and then also do lung function tests, that was the intention'* (P009).

Similar to respondent P009, respondents seem fairly stoic about this particular development - not very enthusiastic, but some are worried that those doing these injections themselves, at home, also means that there will less frequent check-ups and controls at the hospital. As such, this next step meant perhaps to alleviate the burden of treatment might, for some patients, instead increase it.

Experiencing effects of biologicals

The respondents for who benralizumab is working well are all positive about the effects - it allows them to resume normal life, to reboot social life and societal participation. P007 can, again, do the dusty things at the petting zoo he likes to do, P001 can pick up her household again. And that effect is usually achieved very soon after the first injection:

> *'R: Well, that first injection I got, I had to stay for two hours in the ward. And I came home that day and I was so terribly tired. I got a fever and I slept a lot and the next day I felt so good, I think well this I haven't had in years! I had air, energy, I think what is this magic potion?'* (P003).

For P003, the day after the first injection the effects of benralizumab were immediately noticeable. Interestingly, the common reaction respondents provide is not about rejoicing to be able to do something extra, or something, new, but instead about regaining what has been lost ('this I haven't had in years'), and seemed to have recovered, very suddenly. This very sudden, and for most also quite recent, success is joyful, but also experienced as rather precarious. Again P003 speaking:

> *'but the last two times that I have had the lung-function the results were less good, and I am now troubled by everything; I am again really tired and sleepy, my muscles hurt, my joints, and especially the strength in my feet knees, elbows, shoulder and hand diminishes and we still don't know what it is … '* (P003).

The effects of the biological seems to be waning for P003, she notes that as the eight-week period between injections expires, the effect appears to diminish, and the positive effect is not for all respondents to be had – the miracle-cure is not a universal fix. Respondent P002 mentions her frustration that the biologicals do not really seem to affect her:

> *'Inhalers and the other medication did not do much anymore, so then we searched for another possibility. Xolair came into the picture, so for five years I had that, but I was admitted to the hospital quite a few times, but in between I still have had very good periods. And that was also the only biological so far, because I have had five or six, which I think helped me* […] *but good, in November I will start a new one'* (P002).

P002 has been taking biologicals since they have become available, generally to no avail. It is striking that she does pin her hopes on the next and new one (dupilumab). So, whereas respondents can experience biologicals as a being very effective, such experience is always contextualized within their existing experiences of the burden of disease and treatment. The alleviating effect of biologicals is in this way a relative experience; most respondents continue to need prednisone and inhalers, continue to need to make lifestyle changes. In that sense, the biologicals are really an 'add-on' treatment, an extra - but an important '*last straw*' to be grasped with both hands (wife of P010). Perhaps because of this 'last straw' approach to the biologicals, only a few respondents talk explicitly about (possible) side effects of benralizumab. For instance, P008 mentions to experience heavy sweating. Such side-effects appear, however, to be experienced as a relatively light burden especially in comparisons made to the side-effects of the heavy use of prednisone. For the respondents for whom biologicals are effective the main positive effect they mention is to be able to significantly reduce or stop the use of prednisone, thus minimizing or completely getting rid of its side-effects. For the few respondents (P004, P010) for whom the burden of disease was low, they experienced few symptoms except for a persistent cough, the relative effect of benralizumab is much less severe, and as such also their experiences of this burden.

Worries?

Almost all respondents are aware of the lack of scientific understanding of the long-term effects of the use of biologicals. While these effects matter to respondents, respondents do not seem to worry too much about them - this is striking, because as it seems now, they will have to receive this injection every two months for the rest of their lives. But given the large quantities and high frequencies of medication, and the side effects of prednisone that most respondents are used to, this uncertainty seems a relatively small burden of treatment to bear. The possibility that it negatively effects the immune system is a matter that a number of respondents do explicitly question, but respondents do not use such a far-flung time horizon in their interviews. Instead, the time-horizon they work with is much closer to now, it is about the fact that she is now able to lift her grandson up the stairs (P008):

> *'R:* [...] *I do not know the long term* [effects], *but I also do not know what will be wrong with me in the next month. So, let's try it, after the first injection I have a three-year-old grandson who was sleeping and I want to get out of the car and I live in a flat and I walk up in one go with him in his arms* [...] *and I walked in one and my husband says; 'what are you doing?' And I say: 'I don't know either'* [laughter] (P008).

Other respondents mention for instance to be simply happy to be going on a holiday (P003). Exactly how such effects may play out at a later moment is much less relevant, for now.

4 Conclusions

In this study we have explored the everyday life of patients with severe asthma in relation to the use of biologicals, using benralizumab as case in point. The main motivation for this exploration was the current lack of empirical insight into the everyday experiences of patients living with severe asthma and using biologicals. To contribute to this knowledge, we have asked two main questions: 1) How do patients with severe asthma experience their daily life? and 2) How do patients with severe asthma experience the care they receive, and specifically the use of benralizumab, within the context of their daily life? We have approached these questions through a multi-method qualitative study in the Netherlands using a targeted review of available international literature, an analysis of existing patient-stories (ego-documents), two interviews with healthcare professionals and ten interviews with patients suffering from severe asthma. Conceptually we have focused our analysis on exploring patients' experiences of the burden of disease and burden of treatment for severe asthma and the impact biologicals have on these experiences.

4.1 Literature review

Existing literature on the relatively small group of patients living with severe asthma is often of a clinical, technical and epidemiological nature. Little is known and published about patients' experiences of living with severe asthma, and even less is known about how these patients consider the use and effects of biologicals (Eassey et al. 2018). The literature that does focus on these issues describes how the burden of disease of severe asthma moves beyond the boundaries of the experience of the symptoms (shortness of breath, coughing, pain in the lungs, fatigue, etc.) to that of troubles in (intimate) social interaction and patients' societal participation. Social interaction is especially made difficult as a result of the invisibility of severe asthma, the relative unpredictability of exacerbations, and the common notion of asthma as a relatively mild disease.

The burden of treatment for patients appear to consist of the regular use of medication with risks of side-effects and life-style changes, focused on issues such as weight management, not smoking, and avoiding triggers at work, at home, and in everyday social life. Treatment also includes many interactions with healthcare professionals, just as repeated emergency visits to, and repeated and long stays in, revalidation centres and hospitals. While adherence in everyday life is notoriously difficult for these patients, authors are often critical of self-management strategies. Existing literature especially calls for patient empowerment in developing and executing such strategies. However, the main impetus for patients to balance the burden of disease and treatment is said to consist of the need to enhance autonomy in everyday life, and control over their disease. This balancing work combines an ambivalence to medication with somewhat of a disconnect between the clinical realities and patients' everyday lived realities, for instance, what patients consider to be control does not necessarily match clinical definitions.

On severe asthma patients' experiences with add-on treatments such as omalizumab, mepolizumab, reslizumab benralizumab, and dupilimab for severe asthma the literature is scarce. However, it is found that biologicals' clinical benefits lie in is in reducing (risks of) severe exacerbations, effects on day-to-day symptoms and quality of life are said to be modest. In all, we find in the literature that biologicals for severe asthma, if and when they work for the patient, appear to have a significant positive impact on the burden of disease (less symptoms, less risk of severe exacerbations) and the burden of treatment (less need of OCS, less side-effects, less interactions with healthcare professionals, etc.). The lived experience of such effects is however explored very little – the ego-documents and our interviews provide us with clues as to the structure of these experiences.

4.2 Interviews and patient experience stories

The qualitative data in this study on patients' experiences of living with severe asthma corresponds to much of the observations made earlier in the literature. For respondents and authors of the ego-documents, the burden of disease appears intense, overwhelming and sometimes paralyzing. Respondents narrate often long journeys towards a correct diagnosis, including misdiagnoses and unnecessary surgical interventions, and the loss of family, friends and paid work in the process. Similarly, the burden of treatment mentioned by the respondents focuses on the dependency on medication and the many interactions with healthcare professionals. These interactions are experienced as disempowering when, e.g. communication between specialists is faltering, but generally our respondents show high trust in the professionals currently treating them. As expected, in particular the need to use, and side effects of, oral corticosteroids are dominating how respondents discuss their treatment. Respondents have had many experiences of being hospitalized or in need of long revalidation treatments in places such as Davos. Balancing this burden of disease and treatment is often very challenging for all respondents – as the literature suggests we find how respondents aim to (re)gain control over their everyday lives, lives that are framed by breathlessness and fatigue, and often fail to bring this balance about. The 'stigma' of asthma as being a relatively mild disease is an issue respondents also comment on. Respondents mention to strictly control, and limit, with whom they share their diagnosis.

Biologicals such as benralizumab are quite new for respondents. Respondents have learned about biologicals chiefly through their current specialists, but in some cases (regional) media and celebrities helped as well. For the respondents for whom the biologicals work the relative positive impact on both the burden of disease and treatment appears to be high. Respondents mention how both the burden of disease (more able to breath, less fatigue, no exacerbations) and of treatment (less OCS, less inhalers) are lightened significantly – often quite directly after the very first injection. But respondents are generally cautious in their embrace of biologicals and in expressing hope for the future which may be related to their previous turbulent patient journeys. This tentative position and cautionary approach seem justified in that we have also interviewed respondents for whom biologicals do not seem effective, or appear to becoming less effective over time, thus continuing or getting back into an everyday life dominated by a less well-controlled severe asthma. For these patients both the burden of disease and treatment remain high despite the biologicals.

The burden of treatment of the biologicals is scarcely mentioned by respondents. With benralizumab mainly consisting of a bimonthly injection, respondents mainly comment – when prompted - on their wait in the hospital after the injection and on the travelling back-and-forth to the hospital to get their injection. Most respondents are knowledgeable of, though quite stoic about, the relatively new development of self-injecting. One respondent notes to appreciate the regular check-ups and controls that accompany a visit to the hospital, fearing their loss when she needs to inject herself. The relative burden of treatment with biologicals seems particularly low in contrast to the experienced side-effects of OCS; potential side-effects of biologicals are mentioned by only a few respondents. Respondents are generally aware, though appear not very worried, of the lack of knowledge of long-term effects of using biologicals – some respondents do wonder about effects on their immune-system or about the question if they are now dependent for life on this medicine.

Biologicals, in this sense, appear as an 'add-on' treatment in respondents' everyday lives. As a for now cautiously optimistic addition to, or next step in, a (for most respondents) much longer, convoluted and emotionally complex process of living with severe asthma. While biologicals are sometimes considered a 'last straw', for most respondents this process, for sure, has not reached its desired endpoint, even though effective biologicals enable respondents to regain control and autonomy to a for patients unexpected and sometimes astonishingly large extent. Respondents joyfully mention to be able to rejoin their families in normal activities or reboot their societal participation because the biological allows for a broader tolerance for triggers. The contrast with respondents for whom biologicals are not effective is, in this way, very striking.

4.3 Recommendations

Patients suffering from severe asthma are a relatively small group of patients. The suffering from severe burdens of disease and treatment in these patients is not easily recognized as a result of the invisibility of symptoms to outsiders, the unpredictability of exacerbations and the 'stigma' of asthma as being a mild disease. Biologicals, such as benralizumab, appear to offer hope and provide a solution for a considerable part of this population, albeit that these expensive medications offer no structural solution to the disease and long-term effects are insufficiently known. For respondents, showing a good treatment response to biologicals, such concerns appear to be minor issues compared to the relative high gains in diminishing burden of disease and treatment. It seems interesting and relevant for future research to gauge if and how such experiences develop over time as patients work with biologicals over a more extended period. Also, future research might focus more on patients not responding to treatment with biologicals or other add-on treatments and the consequences of this fact for their everyday lives.

Patients for whom biologicals are effective appear to regain significant levels of control and autonomy in their everyday lives. For them, severe asthma no longer seems to be the dominating force structuring interactions and relations. However, these patients' everyday lives still appear to be considerably affected by their previous experiences in- and outside of healthcare practice. Respondents' embrace of biologicals and their newfound breath is cautiously optimistic at best. Care should therefore continue to focus on coping and pay attention to the burden of disease and treatment and how these can be alleviated. How this should be done is something, we would argue, to be established in dialogue between patients and their caregivers. One could consider for instance the acceptance of the finding that patients may not be willing, or able, to modify certain aspects of their everyday lives. Or, to consider the effects of the relatively new development of self-injecting biologicals at home not only in terms of efficiency. For some respondents this development seems to increase their burden of treatment not only because of having to inject themselves but also because interactions with healthcare professionals are becoming scarcer.

These considerations also hold for the patients suffering from severe asthma for whom biologicals are not effective. These patients remain rather invisible to the broader public and socially isolated amongst others as a result of the 'stigma' of their disease. The efficacy of biologicals potentially obscures this group even more – as attention and funds seem drawn to its success and its further development. It seems important, on the level of health policy, care and clinical research, to ensure that a concrete focus on improving the everyday lives of all patients suffering from severe asthma is maintained.

5 Samenvatting (Dutch summary)

In deze studie hebben we het dagelijks leven van patiënten met ernstig astma onderzocht in relatie tot het gebruik van zogeheten 'biologicals', met benralizumab als voorbeeld. De belangrijkste reden voor deze verkenning was het gebrek aan inzicht in het dagelijks leven van patiënten met ernstig astma die biologicals gebruiken. Om aan dit inzicht bij te dragen hebben we twee vragen gesteld: 1) Hoe ervaren patiënten met ernstig astma hun dagelijks leven? en 2) Hoe ervaren patiënten met ernstig astma de zorg die zij ontvangen, en met name het gebruik van benralizumab, in de context van hun dagelijks leven? We hebben deze vragen beantwoord door middel van een kwalitatief onderzoek. Dit bestond uit een analyse van beschikbare internationale literatuur, een analyse van bestaande geschreven Nederlandse patiëntverhalen (egodocumenten), twee interviews met zorgprofessionals en tien interviews met patiënten met ernstig astma. Onze empirische analyse richtte zich op het beschrijven van de ervaringen van patiënten met de ziektelast ('burden of disease') en behandelingslast ('burden of treatment') voor ernstig astma en de impact die biologische geneesmiddelen hebben op deze ervaringen.

5.1 Literatuuronderzoek

Er is weinig aandacht in de literatuur voor de ervaringen van de relatief kleine groep patiënten met ernstig astma. De literatuur die zich hier wel over buigt beschrijft hoe de ziektelast van ernstig astma vooral bestaat uit symptomen (kortademigheid, hoesten, pijn in de longen, vermoeidheid, enz.). Deze last omvat ook problemen in (intieme) sociale interactie en in de maatschappelijke deelname van patiënten. Sociale interactie, bijvoorbeeld met vrienden of op het werk, wordt vooral lastig voor patiënten als gevolg van de onzichtbaarheid van ernstig astma, de relatieve onvoorspelbaarheid van exacerbaties en het algemene beeld van astma als een relatief milde en goed behandelbare ziekte. De behandelingslast voor patiënten met ernstig astma lijkt te bestaan uit het regelmatig gebruik van medicatie, met risico's op forse bijwerkingen, en leefstijlveranderingen gericht op zaken als gewichtsbeheersing, niet roken en het vermijden van triggers. De behandeling omvat veel contact met zorgprofessionals en regelmatige bezoeken aan revalidatiecentra en ziekenhuizen. Hoewel bekend is dat therapietrouw moeilijk is voor deze patiënten, is de literatuur vaak kritisch op bestaande zelfmanagementstrategieën die vooral een klinisch beeld van het dagelijks leven hanteren. Patiënten staan echter vaak ambivalent ten opzichte van hun medicatie, onder andere vanwege de bijwerkingen, en behouden veelal een zekere afstand tussen hun alledaags leven en de klinische realiteit van de longarts. Patiënten slaan zo een balans tussen de ziektelast van ernstig astma en de behandeling daarvan, voornamelijk vanuit een streven om de autonomie in het dagelijks leven te vergroten en enige controle over de ziekte te hebben.

Er is nog minder bekend over hoe patiënten met ernstig astma denken over het gebruik en de effecten van biologicals, zoals omalizumab, mepolizumab, reslizumab benralizumab en dupilimab. Het lijkt wel duidelijk dat de klinische voordelen van biologicals voornamelijk liggen in het verminderen van (risico's op) ernstige exacerbaties. Effecten op de dagelijkse ervaring van symptomen en de kwaliteit van leven zouden positief maar bescheiden zijn, zo ook op de ervaren ziektelast. Dit positieve effect uit zich ook in de ervaring van de behandelingslast (minder behoefte aan prednison, minder bijwerkingen, minder contact met zorgprofessionals, enz.).

5.2 Bevindingen uit interviews en verhalen van patiënten

Onze empirische bevindingen over het dagelijkse leven van patiënten met ernstig astma komen grotendeels overeen met de literatuur. De ervaren ziektelast lijkt intens, overweldigend en werkt soms verlammend. Respondenten vertellen over langdurige zoektochten naar een juiste diagnose, het verlies van contact met familie en vrienden en betaald werk. De door onze respondenten en auteurs van egodocumenten ervaren behandelingslast wordt vooral veroorzaakt door de afhankelijkheid van medicatie en de vele bezoeken aan zorgverleners. Deze contacten met zorgverleners worden als negatief ervaren wanneer bijvoorbeeld de communicatie tussen specialisten hapert of een huisarts de kennis van een respondent over haar eigen lichaam niet serieus neemt. Over het algemeen hebben onze respondenten echter veel vertrouwen in de specialisten en verpleegkundigen die hen nu behandelen. De behandelingslast wordt voor een belangrijk deel ook veroorzaakt door de bijwerkingen van orale corticosteroïden (prednison). Daarnaast hebben respondenten veel ervaring met ziekenhuisopname en langdurige revalidatiebehandelingen op plaatsen zoals Davos. Het algemeen beeld van astma als een relatief milde en goed te behandelen ziekte kan de ziektelast ook vergroten als dit betekent dat de ernst van ernstig astma onderschat wordt. Over het algemeen vinden wij, net als eerder in de literatuur beschreven, hoe respondenten ernaar streven controle te (her)winnen over hun dagelijkse leven en ziekte en hierin vaak worstelen met de balans tussen de ziektelast en die van de behandeling.

Biologicals zoals benralizumab zijn vrij nieuw voor respondenten. Respondenten hebben vooral via hun huidige specialisten kennis gemaakt met biologicals, maar in sommige gevallen hebben ook (regionale) media en beroemdheden zoals Bennie Jolink geholpen. Voor de respondenten voor wie de biologicals werken lijkt de impact op zowel de ervaren ziektelast als die van de behandeling relatief positief te zijn. Respondenten vertellen hoe zowel de ziektelast (beter kunnen ademen, minder vermoeidheid, geen exacerbaties) als behandelingslast (minder prednison, minder puffers) aanzienlijk worden verlicht - vaak vrijwel direct na de allereerste injectie. Respondenten zijn over het algemeen voorzichtig in het positief benaderen van de biological die ze gebruiken, ook zijn ze behoedzaam in het uiten van hoop voor de toekomst. Mogelijk houdt dit verband met de eerder ervaringen die patiënten in hun lange zoektocht hebben opgedaan. De voorzichtige kijk op biologicals lijkt gerechtvaardigd in die zin dat we ook respondenten gesproken hebben voor wie de biologicals (nog) niet werken, of over tijd minder goed lijken te werken. Voor deze patiënten blijft de ervaren ziektelast en behandelingslast onverminderd hoog.

Respondenten lijken maar beperkt last te ervaren van de behandeling met biologicals. De behandeling met benralizumab bestaat hoofdzakelijk uit een tweemaandelijks injectie, en respondenten geven vooral commentaar op het wachten in het ziekenhuis na de injectie en op het heen en weer reizen naar het ziekenhuis. De meeste respondenten zijn op de hoogte van de relatief nieuwe ontwikkeling van zelfinjectie en zijn hier relatief stoïcijns over. Eén respondent merkt op dat zij de regelmatige controles die gepaard gaan met een bezoek aan het ziekenhuis op prijs stelt, en vreest deze te verliezen wanneer zij zichzelf moet injecteren. De relatieve belasting van behandeling met biologicals lijkt zo vrij laag, vooral in vergelijking tot de ervaren bijwerkingen van prednison. Mogelijke bijwerkingen van biologicals worden door slechts enkele respondenten genoemd. Respondenten zijn zich over het algemeen wel bewust van het gebrek aan wetenschappelijke kennis over de langetermijneffecten van het gebruik van biologische geneesmiddelen, maar zij maken zich daar niet al te grote zorgen over. Sommige respondenten vragen zich wel af wat de effecten op hun immuunsysteem zijn, en of zij nu voor het leven afhankelijk zijn van dit geneesmiddel.

Biologicals zijn voor respondenten een waardevolle toevoeging aan de behandeling. Effectieve biologicals stellen de respondenten in staat om voor hen soms onverwacht grote mate van controle over de ziekte en autonomie in het alledaags leven terug te winnen. Respondenten vertellen dat ze weer volwaardig mee kunnen draaien in hun gezin, of werk weer enigszins kunnen oppakken omdat de biological een grotere tolerantie voor triggers geeft. Het contrast met respondenten voor wie biologicals niet effectief zijn, is hierin opvallend. Aan de andere kant wordt de behandeling door onze respondenten vooral voorzichtig optimistisch benaderd. De behandeling met biologicals staat niet los van een (voor de meeste respondenten) veel langer, ingewikkeld en emotioneel complex proces van leven met ernstig astma. Hoewel biologicals soms als een 'laatste strohalm' worden beschouwd, heeft dit proces voor de meeste respondenten niet het gewenste eindpunt bereikt.

5.3 Aanbevelingen

Patiënten met ernstig astma zijn een relatief kleine groep patiënten. De ernstige ziektelast en door patiënten ervaren last van de behandelingen worden niet direct door buitenstaanders herkend als gevolg van de onzichtbaarheid van symptomen, de onvoorspelbaarheid van exacerbaties en het algemeen beeld van astma als een milde ziekte. Biologicals, zoals benralizumab, lijken hoop te geven aan deze groep patiënten en een concrete oplossing te bieden voor het lijden van een aanzienlijk deel van deze populatie. Maar biologicals zijn dure medicijnen en bieden geen structurele oplossing of genezing voor de ziekte. Ook de effecten op lange termijn zijn nog onbekend. Voor respondenten die goed op de behandeling met biologicals reageren lijken dergelijke zorgen van ondergeschikt belang te zijn aan de relatief hoge winst die biologicals nu bieden. In toekomstig onderzoek lijkt het interessant en relevant om na te gaan of en hoe dergelijke ervaringen zich in de loop van de tijd ontwikkelen als patiënten gedurende langere tijd met biologicals werken. Ook zou toekomstig onderzoek zich kunnen richten op patiënten die niet reageren op behandeling met biologicals, en op de consequenties van dit gegeven voor hun dagelijks leven.

Patiënten voor wie biologicals effectief zijn lijken in hun dagelijks leven significante niveaus van controle en autonomie terug te winnen. Voor hen lijkt ernstig astma niet langer bepalend te zijn in sociale interacties en relaties, maar het dagelijkse leven van deze patiënten wordt nog aanzienlijk beïnvloed door eerdere ervaringen in en buiten de zorg. De kijk van respondenten op biologicals is hoogstens voorzichtig optimistisch te noemen. Het lijkt daarom van belang dat de zorg voor deze groep zich blijft richten op coping en aandacht voor het verminderen van de ziekte en behandelingslast. Dit zou concreet vormgegeven moeten worden in de interactie tussen patiënten en hun zorgverleners. Hierbij zou men bijvoorbeeld kunnen denken aan de erkenning van de bevinding dat patiënten niet altijd bereid of in staat zijn om bepaalde onderdelen of aspecten van hun dagelijks leven aan te passen, zoals het al dan niet houden van huisdieren. Ook kan men proberen de effecten van de relatief nieuwe ontwikkeling van zelfinjectie van biologicals niet alleen in termen van efficiëntie te zien. Voor sommige respondenten lijkt deze ontwikkeling juist een toename van de ervaren behandelingslast omdat interacties met zorgverleners minder zullen worden.

Bovenstaande overwegingen zijn ook relevant voor patiënten met ernstig astma voor wie biologicals niet effectief blijken. Deze patiënten blijven tamelijk onzichtbaar voor het bredere publiek en sociaal geïsoleerd onder andere door het 'stigma' van hun ziekte. De grote effectiviteit van biologicals vertroebeld mogelijk nog meer het zicht op deze groep omdat aandacht en beperkte middelen veelal worden gericht op het succes en de verdere ontwikkeling ervan. Op het vlak van gezondheidsbeleid, zorgpraktijk en klinisch onderzoek lijkt het daarom belangrijk om ervoor te zorgen dat er aandacht blijft voor het verbeteren van het dagelijks leven van alle patiënten met ernstig astma.

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