Patients beliefs on intravenous and subcutaneous routes of administration of biologics for severe asthma treatment: A cross-sectional observational survey study

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**ABSTRACT**

**Background:** Understanding how patients generate preferences for administration route alternatives may improve health-care delivery and clinical outcomes. Recently, novel biological therapies with subcutaneous (SC) and intravenous (IV) administration routes have been approved for severe uncontrolled asthma. The aim of our study was to assess the preferred route of biologic therapy administration and related beliefs among patients with severe uncontrolled asthma.

**Methods:** We conducted a cross-sectional observational survey study. Patients answered an anonymous, self-administered questionnaire after an outpatient visit in pulmonary disease clinics located throughout Italy. Socio-demographic and clinical information together with the 12-Item Short Form Survey (SF-12), Work Productivity Impairment Scale and the medical resources utilization module of the Health & Work Survey were collected. Patients beliefs and preference towards SC and IV administration were investigated by means of an ad hoc 13 item questionnaire.

**Results:** The main findings: 150 patients fulfilled the inclusion criteria and completed the questionnaire (47.3\% males). Preference for IV and SC administration was 18.7\% and 81.3\%, respectively. Compared with patients preferring SC formulation, patients that favored IV were older (p = 0.04), less likely to escalate corticosteroid dose (p = 0.03) and had emergency room (ER) access (p = 0.009) during asthma exacerbations. Patients felt that SC was more convenient than IV, but this belief was not associated with higher likelihood of preferring SC administration. IV formulations were more likely associated with quicker and more effective drug action (p = 0.0001), procedural safety and medical oversight (p = 0.0002) and social support (p = 0.007). Predictors of IV preference were represented by the association of worse asthma control and increased use of ER services, and by beliefs toward formulation effectiveness/efficiency in reducing symptoms (p = 0.04 and p < 0.0001, respectively). The model achieved excellent discrimination of administration route preference (area under the curve = 0.87).

**Conclusions:** Preference is guided by partially misleading beliefs, which may generate wrong expectations that in turn can affect treatment satisfaction and adherence. Convenience and efficacy beliefs for drugs with different routes of administration always should be discussed with patients to achieve informed shared-decision making.

**Trial registration:** Not applicable.

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Methods

Design and setting

We conducted a cross-sectional observational survey study. Patients answered an anonymous, self-administered questionnaire after an outpatient visit in pulmonary disease clinics located throughout Italy. We enrolled adult patients younger than 75 years of age, without chronic respiratory tract comorbidities (i.e. chronic obstructive pulmonary disease, pulmonary fibrosis, emphysema, and cancer), and we restricted study inclusion to patients with poorly controlled asthma as determined by Asthma Control Questionnaire 6-item score (ACQ-6) $\geq 1.5$.26–28 Despite use of medium/high dose of inhaled corticosteroids/beta-adrenergic agonists combinations in the previous 12 months. Patients receiving a biologic therapy for severe asthma were not excluded from the study. No personal identifiers can be deducted from the answers to the questionnaire. After filling in the questionnaire, patients put the survey packet into an anonymous envelope and returned it to a study assistant so that patients’ answers could not be matched to subjects’ identity. According to the Italian regulation,29 cross-sectional survey research based on anonymous questionnaires do not require ethical committee approval.

Measures

The questionnaire packet included a brief screener questionnaire (BSQ) tapping socio-demographic (i.e. age, geographic region, gender) and clinical information (diagnosis of asthma, presence of any other lung diseases, assessment of asthma control, concurrent asthma related treatments and routes of administration, remedies to exacerbations occurred in the previous 12 months). Responses to the BSQ were used to determine study eligibility. Furthermore, we collected information concerning patients’ history of exacerbations according to expert consensus definition30; in order to facilitate patients’ recall of exacerbation episodes occurred in the previous 12 months we provided the event definition as a primer: “Exacerbations - commonly referred to as asthma attacks or acute asthma - are episodes of progressive increase in shortness of breath, cough, wheezing, chest tightness, or a combination of these symptoms which occur despite the regular assumption of usual therapy. When an exacerbation occurs, it is required to assume a systemic corticosteroid treatment or at least a doubling of existing dose for maintenance oral corticosteroid and/or a hospitalization and/or an emergency department visit”. We asked to report the frequency of episodes occurred in the past 12 months and recourse to hospitalization, emergency room visits, corticosteroid therapy initiation or dose escalation. We also collected employment status according to the International Labour Office definition and past/current exposure to potential occupational or environmental risk factors for asthma.

Additionally, the questionnaire packet included the 12-Item Short Form Survey (SF-12), Work Productivity Impairment Scale, and the medical resources utilization module of the Health & Work Survey.31–33 (Additional file 1).

Patients beliefs on IV and SC route of administration of biologic therapy

Since no valid scale tapping patients’ beliefs toward IV/SC administration route exists, we were forced to devise an ad hoc scale for the study. Seventeen items (i.e. beliefs) were generated by literature review and expert opinion (Additional file 2). Before answering the beliefs scale, patients were primed with statements describing the indication for biologic therapy and the procedure involved for both IV and SC administration modality (Additional file 3). Patients were asked to rate how much they believed that either one of the two administration modalities was characterized by the 17 attributes generated, which were pertaining to four factors: a) procedural safety and medical oversight (e.g. “It allows a closer medical oversight during drug administration”); b) efficacy and speed of action (e.g. “It allows greater speed of action of the drug (the drug takes effect earlier”) ; c) social support (e.g. “It allows to have closer
relationships with medical staff”); d) convenience of administration (e.g. “It allows less time spent managing asthma”). Ratings occurred through a bipolar scale of evaluation (−2, strong belief that attributes specifically characterize SC; 0 = attributes characterize both modalities equally; 1 = mild belief that attributes specifically characterize IV; 2 = strong belief that attributes specifically characterize IV). The content of the 13 selected items were respectively computed for continuous or categorical variables.

Additionally, patients were asked to choose either IV or SC route of administration in case their attending physician would have prescribed them a biologic therapy (Additional file 3).

### Statistical analysis

Means and standard deviations or absolute and relative frequencies were respectively computed for continuous or categorical variables.

The association between patients’ preference for IV or SC route of administration and socio-demographic and clinical characteristics has been evaluated with t-test or χ² test for continuous or categorical variables respectively. We adopted a stepwise logistic regression (entry criterion: p < 0.030; stay criterion: p < 0.010) to assess independent correlates of IV or SC route of administration. We adjusted the multivariable model for socio-demographic (age, sex, geographic area, employment status, high-risk occupation) and clinical characteristics (disease duration, ACQ-6 score, complexity of treatment regimen, exacerbation remedies, current and previous medication for asthma, medical resource utilization, mental and physical SF-12 composite scores, sleep quality, BMI, work productivity and activity impairment, suffering from allergy, experience with biologic therapy for asthma). P < 0.05 was considered statistically significant.

In order to help facilitate the interpretation of the multivariable analysis and the impact of the cross-interaction observed, we calculated the predicted probability of preferring the IV administration route for ten hypothetical patients with different demographic characteristics, clinical factors and beliefs, based on the estimated parameters of the logistic regression (Table 2). Factor analysis and related reliability concerning beliefs towards IV and SC route of administration are shown in Table 1. Analyses were conducted with SAS 9.4™.

### Results

One hundred and fifty patients fulfilled the inclusion criteria and completed the questionnaire. Table 3 shows socio-demographic and clinical characteristics of the whole sample and the subset of patients who expressed preference for IV (18.7%) or SC (81.3%) route of administration.

In total, half of the sample (50.7%) was currently taking corticosteroid; SC biologic therapy was the current therapy for 32% of patients (among these, 31 subjects (64.8%) were treated with omalizumab, 17 subjects (35.4%) with mepolizumab), whereas 4% had past experience with biologic drugs. Disease duration was 25 years on average (sd = 12.4), which represented about half their lives (48.8 y; sd = 12.1). In the previous 12 months, subjects had access almost twice to the emergency room (ER) and received 4.55 outpatient visits due to asthma-related complications; remedies to last exacerbation mainly consisted in corticosteroid dose escalation (1.76 times).

### Table 2

Hypothetical clinical scenarios illustrating adjusted probability of preferring the IV route of administration.

| Case | ACQ-6** | ER access** | Belief: speed of action** | Adjusted estimated prevalence of preference for IV route of administration |
|------|---------|-------------|--------------------------|---------------------------------|
| A    | 0       | 1           | −1                       | 1%                              |
| B    | −1      | −1          | −1                       | 3%                              |
| C    | −1      | 1           | 1                        | 3%                              |
| D    | 1       | −1          | −1                       | 5%                              |
| E    | 0       | 1           | 1                        | 15%                             |
| F    | 1       | −1          | 0                        | 18%                             |
| G    | 0       | 0           | 0                        | 19%                             |
| (reference) |       |             |                          |                                 |
| H    | 1       | 1           | 0                        | 21%                             |
| I    | 1       | 1           | −1                       | 52%                             |
| J    | 2       | 2           | 2                        | 98%                             |

* Numbers represent increase (1,2) or reduction (−1) of standard deviations from the mean of total sample (ACQ-6 score = 2.62, sd = 0.52; frequency of resorting to ER services in case of exacerbations = 0.96, sd = 0.80; speed of action of drug (belief) = 0.64, sd = 1.46). **Asthma-related treatment regimen held constant at their sample average (Regimen Complexity: 2.12; BMI: 24).
Patients who expressed preference for IV were older (52.7 y vs. 47.9 y; p = 0.04); were less likely to escalate corticosteroid dose (1.25 vs. 1.88, p = 0.03) and to resort to ER access (0.61 vs. 1.04; p = 0.009) during asthma exacerbation; were less likely to use corticosteroid for current management of asthma (4.7% vs. 46%; p = 0.003) and to use inhalatory formulation for current medication (18.7% vs. 72%; p = 0.06). Patients who reported previous or current experience with SC biologic therapy for asthma expressed greater preference for SC route of administration compared to IV formulation (32.7% vs. 3.33%; p = 0.03).

Associations between preferences and beliefs towards IV and SC route of administration are shown in Fig. 1. Overall, patients felt that SC was more likely to access ER in case of exacerbation and more strongly believed that such an administration route would enable quicker and more effective drug action (p = 0.0001), as well as procedural safety and medical oversight (p = 0.0002) and social support (p = 0.007) compared to subjects who expressed preference for SC medication. Statistically significant predictors of preference for IV route administration in the multivariable logistic regression model are shown in Table 4. The interaction between ACQ-6 score and ER use during exacerbation was statistically significant (0.76; p = 0.04). Parameter estimates indicated that the strength of association between asthma control status and the likelihood of preferring IV formulations increased with greater use of asthma-related ER services; additionally, beliefs toward formulation effectiveness/efficiency in reducing symptoms was the only belief score independently associated with patients’ preferences (Table 4). The model achieved excellent discrimination of administration route preference (area under the curve – AUC = 0.87).

In order to simplify the interpretation of regression coefficients we report ten different hypothetical clinical scenarios illustrating estimated probabilities of preferring IV route of administration associated to different values of ACQ-6 score, frequency of resorting to ER services in case of exacerbations, and beliefs toward differential efficacy across administration routes. Body mass index and the number of asthma-related treatments were held constant at the sample average (Table 2). The reference patient in our sample (case G) had 19% probability of preferring IV administration. The probability of preferring IV administration rose as the patients had more intractable disease (i.e. higher ACQ-6 score), was more likely to access ER in case of exacerbation and more strongly believed IV was more effective than SC administration.

Discussion

This study investigated preference and beliefs towards IV and SC routes of administration of biologic therapy among patients suffering from inadequately controlled severe asthma.
Our findings revealed SC formulation was the preferred route of administration, chosen as a hypothetical add-on therapy by more than 80% of participants.

Patients’ beliefs toward procedural safety and medical oversight, social support, efficacy and speed of action were associated with administration route preference in the univariate analysis. However, multivariable logistic regression showed that only beliefs toward efficacy independently affected likelihood estimates. Given the relatively small sample size and the inter-correlation between beliefs dimensions, it may not be possible to disentangle the independent effect of each belief within this study. Even though multicollinearity was moderate in our analysis, we cannot exclude that regression estimates were unstable (i.e. sensitive to small changes) and overly imprecise (i.e. wider confidence intervals due to multicollinearity).

We also showed that patients with less asthma control were more likely to opt for IV formulation, especially when accesses to ER services in case of exacerbations were frequent. Taken together, our results suggest that patients may perceive IV treatment as a more effective drug, reserved for the most severe or difficult-to-control cases.

Since we observed that patients’ beliefs towards route of administration may influence their treatment preferences, it is important to explore in more detail specific beliefs driving patients’ scale scores. Specifically, our results showed that SC formulation was felt as enabling more time for daily activities unrelated to disease care (loading = 0.78), as well as allowing greater convenience compared to IV formulation (loading = 0.73) and was believed to impose less time spent managing asthma (loading = 0.75) and its practical hassles concerned to treatment administration (loading = 0.70). Conversely, IV route of administration was associated with less frequent dose administrations (loading = 0.83), considered faster in reducing symptoms (loading = 0.74) and more effective (loading = 0.52) compared to SC formulation. Such beliefs were stronger for patients who expressed preference for IV administration, and it was the most important predictor of IV preference.

Since only a minority (36%) of our sample reported current or previous treatment with SC biological drugs for asthma, and none had experience with IV biologics, understanding whether observed beliefs may rely on false opinions is crucial to informed decision-making.

Indeed, previous studies investigating preference for IV or SC formulation mostly evaluated patients’ perspective after they switched from one route of administration to another, thus considering directly experienced trade-offs compared to IV formulation, SC was frequently associated with convenience of use since the self-administered procedure resulted in considerable time savings for patients. Conversely, both IV and SC biologic therapy for uncontrolled asthma require a hospital care setting for administration, which may thus virtually eliminate the differences across the two formulations in terms of administration time and organizational burden for the patient; our questionnaire specifically tapped administration time intrusiveness on daily life and organizational burden. Unfortunately, we could not debrief patients’ cognitive answering process to discover how their beliefs were formed. Such understanding is key to delivering appropriate health education and correct unfounded beliefs which may affect treatment expectations, decisions and subsequent treatment satisfaction.

Similar to opinions about convenience, beliefs toward efficacy and speed of action should be challenged against scientific evidence. Few studies compared asthma-related drugs with different administration routes generally showing no statistically significant difference. One notable exception is represented by one randomized controlled trial (RCT) comparing 4 monthly doses of IV reslizumab against SC mepolizumab (12 monthly doses). The authors observed greater asthma control among patients on IV reslizumab compared to the comparators in a subset of severe prednisone-dependent patients with asthma. However, it is not currently possible to discriminate the effect of the active principle and the impact of the administration route.

Other potentially important beliefs dimensions have been investigated. Previous studies assessing experience with IV biologic therapies among Inflammatory Bowel Disease and rheumatology patients, showed satisfaction with IV treatment because it was associated with enhanced social support and closer procedural oversight from health care professionals and physicians. In our study, neither social support nor procedural oversight was felt as a prominent feature of any specific

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**Table 4** Statistically significant predictors of preference for IV route of administration.

|   | Estimates | p     |
|---|-----------|-------|
| ACQ-6 | 1.04 | 0.011 |
| ACQ-6 * ER access | 0.76 | 0.040 |
| ER access (exacerbation remedy) | -0.68 | 0.064 |
| Belief: speed of action | 1.44 | < 0.0001 |
| Number of asthma-related treatment | 0.78 | 0.068 |
| BMI | 0.18 | 0.067 |

Multivariable model adjusted for socio-demographic (age, sex, geographic area, employment status, high-risk occupation) and clinical characteristics (disease duration, ACQ-6 score, complexity of treatment regimen, exacerbation remedies, current and previous medication for asthma, medical resources utilization, mental and physical SF-12 composite scores, sleep quality, BMI, work productivity and activity impairment, suffering from allergy, experience with biologic therapy for asthma).
administration and this may be consequently due to lack of experience with biologic therapy; however, patients preferring IV formulations were more keen to believe that this route of administration would guarantee a greater procedural safety and medical oversight.

Given that asthma-related biologics are all administered in hospital settings, and RCTs have proven both mepolizumab, reslizumab and benralizumab to be safe,\(^{11}\) reasons driving patients’ beliefs should be investigated further.

Finally, this study has some limitations. First, it is a cross-sectional survey, and our patients have been invited to speculate on a hypothetical scenario since, at the time of the survey, no IV formulation was marketed worldwide. As a consequence, we cannot directly infer actual behavior should the patients face a real option. Moreover, we acknowledge that the inclusion of patients with a previous or current experience of biologic treatment may represent a confounder; in this view, the multivariate model was adjusted for treatment regimens and previous biologics use. Indeed, we believe that the study sample could reflect a real life clinical scenario in outpatient clinics that are responsible for the everyday management of patients with asthma. Second, the beliefs toward administration modality scale (BAM) was developed for the study since no existing questionnaire tapped the dimensions of interest. Even though the basic psychometric properties corroborated the suitability of BAM among patients with uncontrolled asthma, further studies should replicate our results. Finally, recruitment was based on a patients’ self-administered screener questionnaire. As a result, we cannot exclude selection bias limiting the generalizability of the study.

Conclusions

This study investigated preferences and beliefs towards IV and SC route of administration among patients with severe uncontrolled asthma reporting limited experience with biologic therapies. We found preference to be guided by partially misleading beliefs, which may generate wrong expectations that in turn may affect treatment satisfaction and adherence; clinicians should be aware of possible cognitive bias in order to provide patients with correct information and health education. Overall, our findings suggest that beliefs toward convenience and efficacy of drugs with different routes of administrations should be formally elicited and discussed during doctor-patient interaction to achieve informed shared-decision making.

Patients with severe asthma are at risk of increased morbidity and have a substantial impact in terms of healthcare utilizations; thus identifying optimal treatment regimen is fundamental.\(^ {20}\) In light of similar efficacy and safety profiles of identified medications, patients’ preference assumes a relevant role thus making a shared decision with clinicians on realistic information essential. Further studies are needed to deeply investigate preference among patients with uncontrolled severe asthma, and to determine their role over compliance, satisfaction and perception of treatment efficacy.

Declarations

Ethics approval and consent to participate

Not applicable. According to the Italian regulation cross sectional survey researches based on anonymous questionnaire do not require ethical committee approval.

Consent for publication

Not applicable.

Availability of data and material

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

PS reports grants and personal fees from Chiesi Farmaceutici, grants from Air Liquide, Pfizer, Almirall, personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, Menarini, Malesci/Guidotti, Mundipharma, Zambon, Berlin-Chemie, Valeas. DR reports personal fees from AstraZeneca and Boehringer Ingelheim. FB has participated as a lecturer, speaker, and/or advisor in scientific meetings and courses under the sponsorship of AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, Dompe, GlaxoSmithKline, Lallemand Pharma, Malesci/Guidotti, Menarini, Mundipharma, Novartis, Teva, and Zambon.

MF, IB and AF declare that they have no competing interests.

Authors’ contributions

PS, IB, AF and FB participated in study design and data analysis; PS, MF, IB, DR, F and FB participated to data interpretation and manuscript and drafting. All Authors critically revised the manuscript and gave final approval.

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Authors’ information

Not applicable.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.waojou.2019.100030.

List of abbreviations

| Acronym | Full Form |
|---------|-----------|
| ACQ-6   | Asthma Control Questionnaire 6-item score |
| BAM     | beliefs toward administration modality scale |
| BSQ     | brief screener questionnaire |
| CS      | subcutaneous |
| ER      | emergency room |
| IL      | interleukin |
| IV      | intravenous |
| SDM     | shared decision making |
| mAbs    | monoclonal antibodies |

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