

A multidisciplinary Delphi consensus on budesonide aqueous nasal spray in managing upper respiratory diseases

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ABSTRACT

Allergic rhinitis (AR), non-allergic rhinitis (NAR), and chronic rhinosinusitis with nasal polyps (CRSwNP) share a type 2 inflammation. Thus, intranasal corticosteroids (INCS) are recommended for managing these diseases. In this regard, budesonide aqueous nasal spray (BANS) has been an effective and safe INCS available for decades. As a recent Delphi consensus and a survey explored the use of topical nasal therapy in practice, a panel of experts promoted a multidisciplinary Delphi consensus on BANS in daily practice. Forty-six Italian expert otorhinolaryngologists, allergologists, and pediatricians participated in the initiative. Twenty-one statements were voted on. There was a large agreement with all statements. Thus, this document proposed a valuable BANS use in managing patients with AR, NAR, or CRSwNP considering the relevant activity on dampening type 2 inflammation. Moreover, the safety profile was considered good, also concerning the bioavailability issue. However, based on the severity of the disease, BANS use should be prescribed as cycles or for prolonged periods. In conclusion, the present multidisciplinary Delphi consensus supported BANS use in upper airway type 2 diseases.

Key words: budesonide aqueous nasal spray, allergic rhinitis, non-allergic rhinitis, chronic rhinosinusitis with nasal polyps, Delphi consensus

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Introduction

Rhinitis and rhinosinusitis are the most important chronic inflammatory disorders affecting the upper airways [1].

Chronic rhinitis may be classified considering the pathogenetic mechanisms, such as allergic and non-allergic [2]. Allergic rhinitis (AR) recognizes a type 2 endotype characterized by a predominance of innate (innate lymphoid cell 2: IL-C2) and acquired (T helper 2: Th2) immunity [3]. This type 2 polarization leads to allergen-specific IgE production (i.e., the sensitization) and eosinophilic infiltration of respiratory mucosa [4]. Conversely, non-allergic rhinitis (NAR) may also display a type 2-driven mucosal infiltration by different types of inflammatory cells (mainly including eosinophil, mast cell, and neutrophil), but always without sensitization [5].

Chronic rhinosinusitis (CRS) includes two main phenotypes based on presence (CRSwNP) or absence (CRSsNP) of nasal polyps [6]. In Western countries, CRSwNP is commonly sustained by a prevalent type 2 immunity [7].

Considering these shared pathophysiologic mechanisms, it is consequential that anti-inflammatory drugs are suitable for managing AR, NAR, and CRSwNP [8]. In this regard, intranasal corticosteroids (INCS) are the most potent medications in dampening airway inflammation and, consequently, relieving related symptoms [9].

Budesonide is a corticosteroid provided with relevant local activity [10]. In particular, budesonide is available as an aqueous nasal spray (BANS) with the therapeutic indication (approved by the Italian regulatory agency) for treating seasonal allergic rhinitis, perennial allergic and non-allergic rhinitis, nasal polyposis (NP), and preventing relapse of NP after surgery. Interestingly, BANS is available in two dosages: 50 and 100 mcg. In addition, multiple schedules are available from 100 to 400 mcg/daily and indicated from six years of age in children.

Three recent reviews presented and discussed the most relevant and recent studies concerning the use of BANS in adults and children with AR and in patients with CRSwNP [11-13].

A recent intersocietal multidisciplinary Delphi Consensus on topical nasal therapy provided a series

of statements on this issue [14]. In particular, there was broad agreement that nasal spray is the most suitable administration device for treating rhinitis and rhinosinusitis, and corticosteroids are particularly recommended for managing patients with AR, NAR, and CRS [14]. In addition, a recent multidisciplinary survey on topical nasal treatments in Italy involved 445 otorhinolaryngologists, pediatricians, and allergologists [15]. This survey demonstrated that INCS are the most frequent (67%) medications used for intranasal therapy [15].

However, these Delphi Consensus and Survey did not go into the details of the individual molecules used in the different diseases for content and the vastness of the topic. Therefore, the steering committee invited the same panel of experts to participate in a new multidisciplinary Delphi Consensus on the practical use of BANS in managing patients with AR, NAR, and CRSwNP. Therefore, the present article reports and discusses the results of this multidisciplinary Delphi consensus.

Methods

Delphi method

We used a modified Delphi method to find a consensus on a list of statements among a panel of expert Italian specialists, including otorhinolaryngologists, pediatricians, and allergologists.

The first round involved a restricted group of independent experts (GC, ILM, and AV) constituting the steering committee that drafted a list of statements to be voted on.

The steering committee requested an interest in participating in some Italian specialists in otorhinolaryngology, pediatrics, and allergology.

The second round involved a group of 46 experts, previously nominated and delegated by 14 scientific societies or selected by the steering committee, who participated in the project concerning topical nasal therapies. This second round consisted of administering the statements approved during the first round. For this purpose, we created a web platform that allowed anonymous voting of all statements. The panel of participants included experts who were also selected based

on their clinical practice (at least ten years of specialized activity) and scientific value (at least ten publications in peer-reviewed journals on this topic in the last five years).

The participants anonymously voted using the same platform.

After collecting and analyzing the second round's results, the steering committee discussed and approved them.

The Delphi consensus process was conducted between November 2024 and December 2024.

Delphi statements

The figures (1-3) present the list of the 21 (previously approved) statements proposed to the participants in the third round. The statements concerned the practical use of BANS.

Delphi assessment

The Delphi Consensus Panel was requested to rate their agreement with each questionnaire statement using a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). Each expert provided individual and anonymous feedback on the statements, considering routine practice and clinical evidence. The number and percentage of participants scoring each item as 1–2 (disagreement) or 4–5 (agreement) was calculated.

The scientific committee then discussed the results in a virtual meeting. For each questionnaire statement, the consensus was considered to have been achieved based on the agreement (score 4-5) of at least 80% of the Consensus Panel and the successive acceptance of the steering committee.

The statistical analysis was descriptive, and a mean score of 4+5 scores was calculated considering the standard deviation.

Results

The first round, voted on by the steering committee, confirmed complete agreement concerning all the statements: a score of 5 was reached for all 21 statements.

The second round included a panel of 46 experts selected by the steering committee. The voting results are reported in Figures 1-4.

Seven statements (6, 7, 8, 12, 15, 17, and 21) obtained the full agreement (100%) of the participants. Ten statements (3, 4, 5, 9, 10, 11, 13, 14, 16, and 19) had an agreement percentage of more than 90%. Finally, four statements (1, 2, 18, and 20) reported an agreement percentage between 80 and 90%.

Consequently, all statements reached a positive consensus, such as > 80%.

Discussion

Allergic rhinitis, NAR, and CRSwNP display a mucosal infiltrate usually sustained by type 2 inflammation [1]. As a result, intranasal corticosteroids are the most powerful medication to dampen type 2 inflammation [16]. Consistently, a multidisciplinary Delphi consensus and a multidisciplinary survey on topical nasal therapy confirmed the relevance of intranasal corticosteroids in managing patients with chronic inflammatory disorders [14,15].

Budesonide is a widely used medication. The present multidisciplinary Delphi consensus would propose a shared approach to its use in daily practice. The multidisciplinary composition of participants may ensure a valuable implementation.

In particular, all statements reached the optimal level of agreement, such as > 80%.

Statement 1 recognized that the traditional AR classification (i.e., seasonal and perennial) is still effective and also endorsed by the recent ARIA guidelines [17]. This classification allows a simple and quick identification of the causal allergen and reflects the seasonality of symptoms.

Statement 2 underlined the possible association between AR and NAR. This comorbidity has relevant implications: e.g., allergen-specific immunotherapy could not be effective in completely relieving symptoms if NAR coexists [18]. In this case, NAR should be considered a possible cause of AIT inefficacy.

Statement 3 confirmed that topical corticosteroids represent the first-line therapy to manage AR and NAR, as stated by most guidelines [17-21]. Indeed,

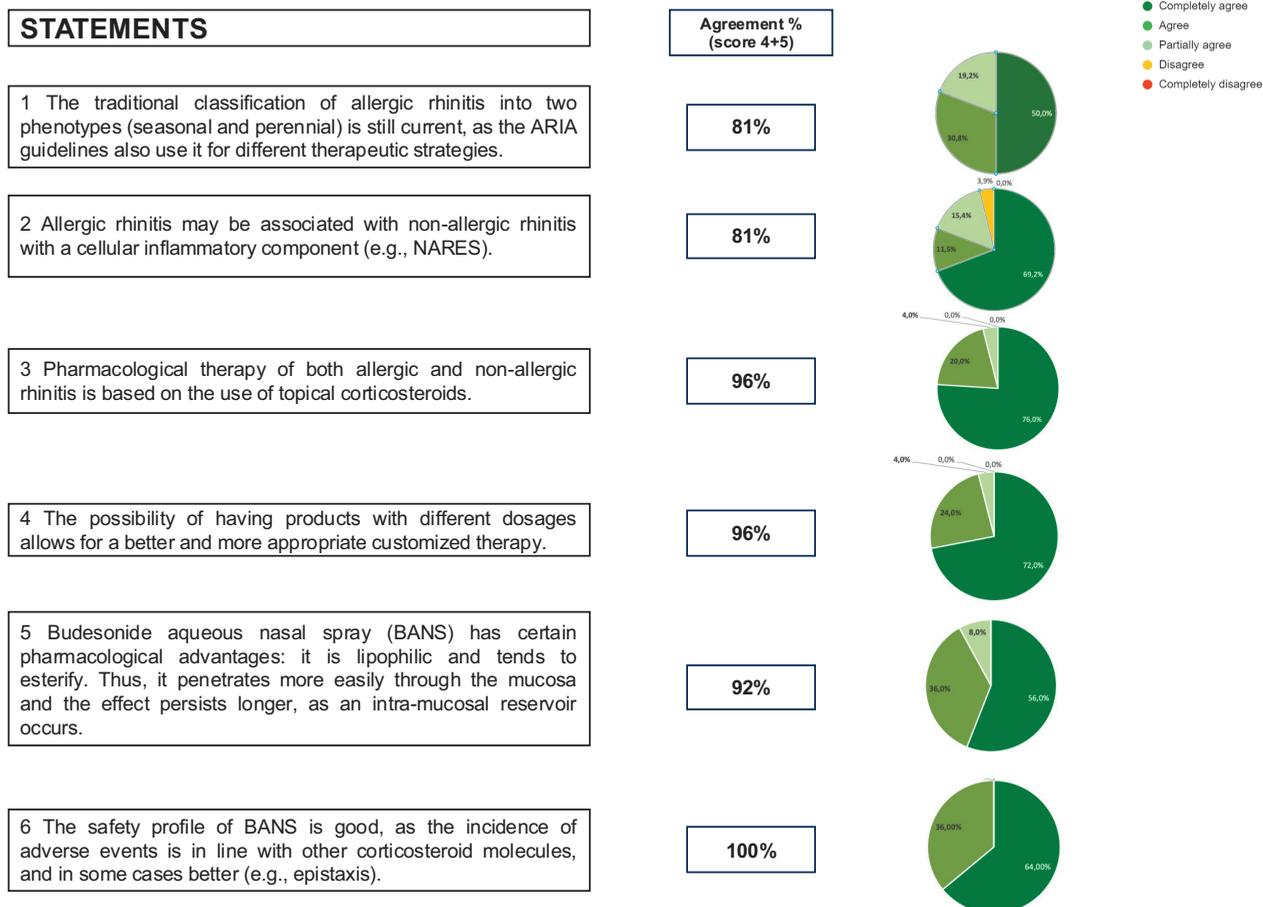


Figure 1. Text and distribution of agreement score for Statements 1-6.

these guidelines stated that intranasal corticosteroids constitute a keystone in treating type 2 inflammation.

Statement 4 collected a wide consensus: intranasal corticosteroids with different dosages allow tailored treatment, as titrating dosage constitutes the basis for personalized medicine. In this regard, BANS offers the possibility of two different packages (50 and 100 mcg) and a posology ranging from 100 to 400 mcg/daily.

Statement 5 stated that BANS has pharmacological advantages, including lipophilic properties and esterification. These two characteristics allow optimal penetration into the mucosa and prolonged activity [11-13]. Participants expressed high consensus about this statement (92%).

Statement 6 concerned BANS' safety profile. The participants fully agreed about BANS' good safety

characteristics, including local (mainly concerning epistaxis) and systemic adverse reactions. In this regard, statement 7 collected a full consensus (100%) about BANS' systemic safety [22].

Statement 8 received full agreement (100%) as it underscored the concept that plasmatic bioavailability requires a correct interpretation considering the area under the curve instead of the peak [23]. This issue has a relevant clinical implication as some concerns were previously proposed about a high plasmatic peak generated by BANS.

Statement 9 concerned the need to consider topical corticosteroids as a treatment requiring reevaluation. Almost all participants shared this concept. Consistently, statement 10 defined that BANS should not be used symptomatically but require a prescription for a

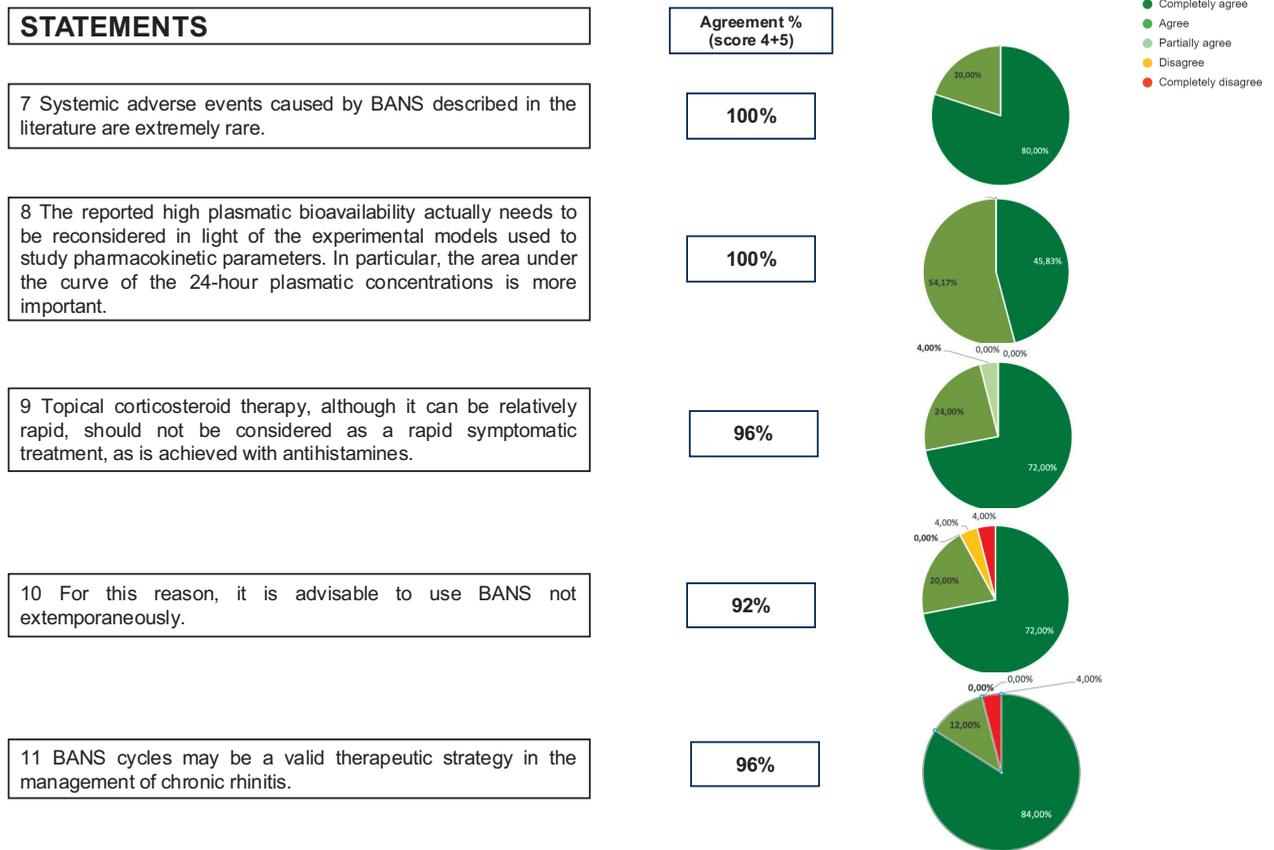


Figure 2. Text and distribution of agreement score for Statements 7-11.

certain period of time (92% of agreement). Also, statement 11 recognized that BANS should be used for treatment cycles (96% of agreement). Statement 12 also proposed the possibility of using BANS continuously during the acute phase of AR, such as pollination peaks: the agreement was full (100%). Therefore, these last statements considered two alternative options: cycles or continuous treatment depending on the severity of type 2 inflammation. In addition, these statements highlighted the importance of not considering BANS as a symptomatic therapy to be used on demand.

Statement 13 concerned CRSwNP and declared that this condition displays type 2 inflammation in Western countries [24]. Almost all participants agreed with this evidence.

Statement 14 was consequential, as it stated that CRSwNP should be managed with intranasal

corticosteroids according to international guidelines EPOS and EUFOREA [25,26]. The consensus was 96%. As a result, BANS represents a valuable option. This statement 15 received full agreement (100%).

Statement 16 concerned the possibility of using topical corticosteroids after nasal polyp surgery to prevent recurrences. The agreement was 96%.

On the other hand, statement 17 declared that biological therapy with anti-cytokine agents modified the management of severe CRS [27]. All participants agreed with this declaration.

Although biologics are effective, intranasal corticosteroids (but those only with the therapeutic indication, including BANS) may be added as an integrated therapy: statement 18. The agreement was 84%. Some experts believe that biologics may be sufficient to manage patients with CRSwNP. However, 92% of participants

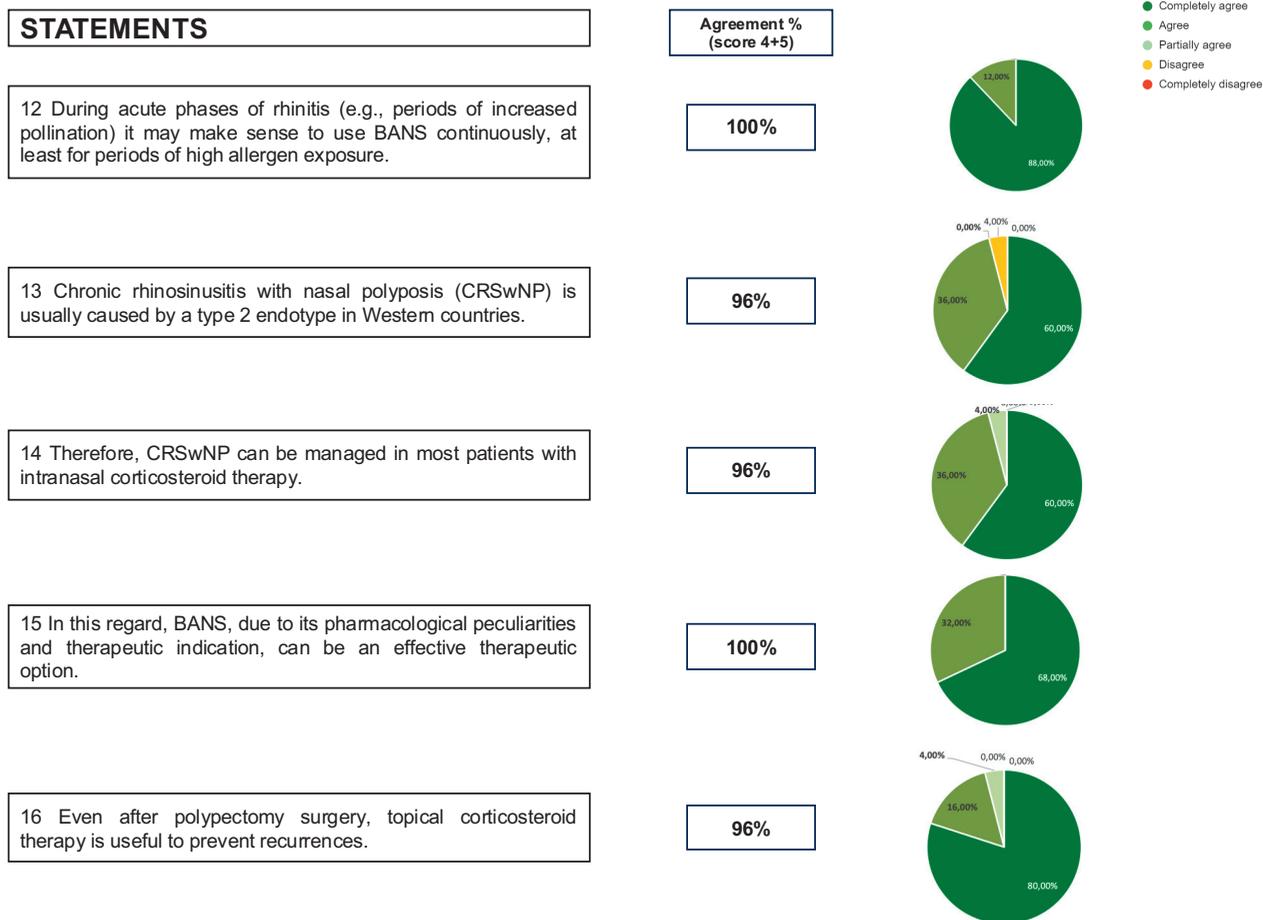


Figure 3. Text and distribution of agreement score for Statements 12-16.

agreed with statement 19, which considered the use of continuous corticosteroids at low dosages. In this regard, statement 20 states that preventive therapy after surgery can be used. The consensus degree was 82%.

Statement 21 remarked on the importance of patient engagement and education about the correct use of intranasal corticosteroids, including device use, as recently reported [28].

Globally, the present multidisciplinary Delphi consensus proposed a series of statements that can be applied in clinical practice. There was a shared agreement about all of them. Thus, the document confirmed BANS as a valuable option for managing patients with AR, NAR, and CRSwNP.

However, this consensus had some limitations, including the limited number of participants and the need for more contributions from the scientific community.

In conclusion, this multidisciplinary Delphi consensus stated that BANS is an effective and safe intranasal medication for managing upper airway type 2 inflammatory diseases. Some safety issues have poor clinical relevance. Conversely, there was considerable agreement about using BANS appropriately, such as prescribing cycles or prolonged schedules.

Lastly, the World Health Organization included budesonide in the 23rd list of Essential Medicines as a unique corticosteroid for treating allergic rhinitis.

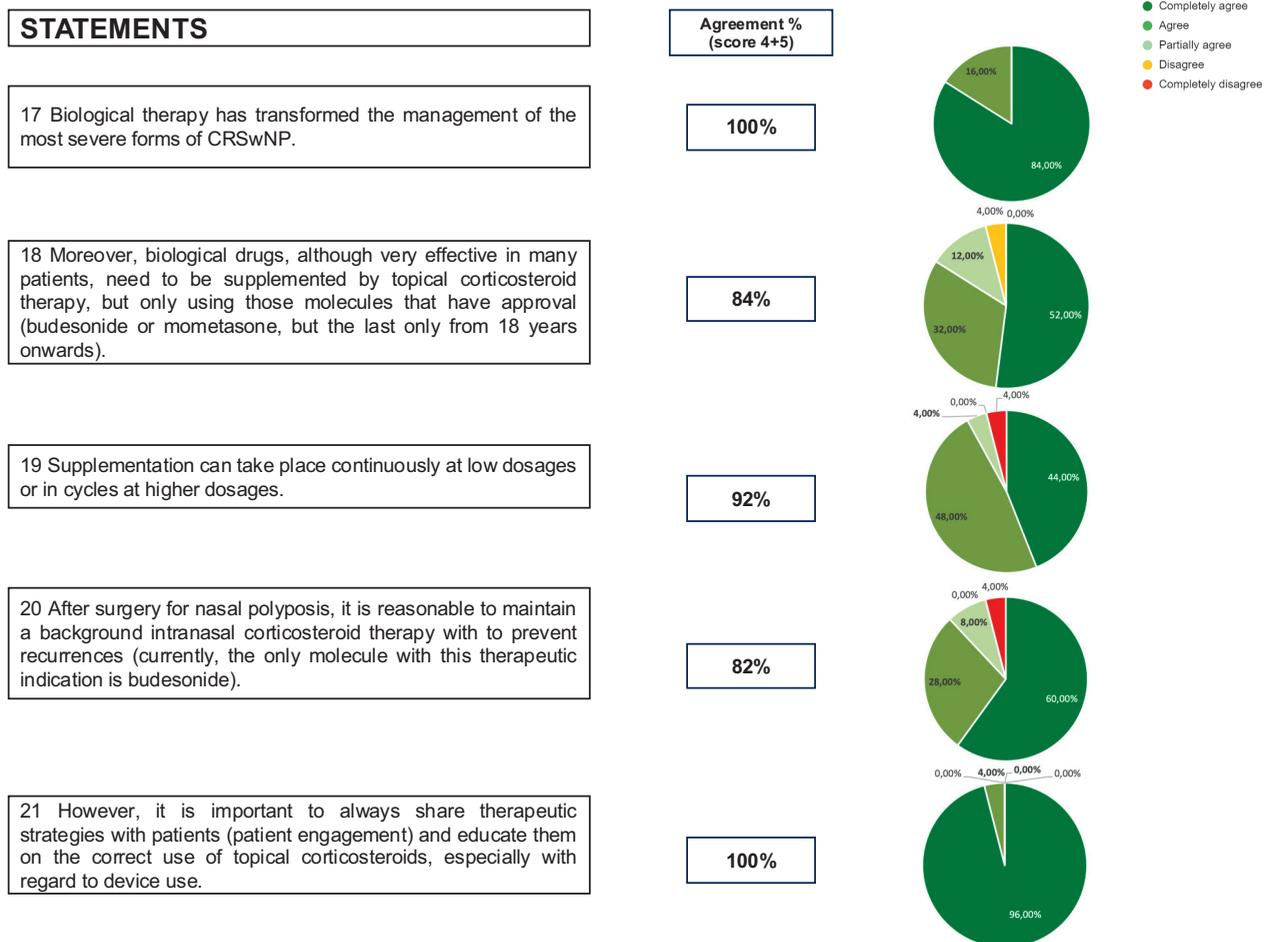


Figure 4. Text and distribution of agreement score for Statements 17-21.

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