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Effectiveness and tolerability of Tonsilgon® N in the treatment of recurrent upper respiratory tract infections in children: a non-interventional study in Russia

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Abstract

Background: Acute upper respiratory tract infections (ARI) in children are quite common and often recurrent. Overuse of antibiotics must be avoided, and thus herbal remedies are a useful therapeutic option, as most ARIs can be treated without antibiotics. The aim of this observational study was to demonstrate the effectiveness and tolerability of the herbal combination preparation Tonsilgon® N in Russian children aged 2–11 years in routine practice.

Methods: In a prospective, non-interventional study a total of 518 paediatric patients (boys and girls) with ARI were enrolled at 14 study sites in Russia (2013 - 2014). Patients must have had at least two episodes of ARI in the last 6 months prior to enrolment (day 1 = visit 1). Tonsilgon® N was given as coated tablets or oral drops in age-corresponding dosages. Treatment duration was approximately 14 days (day 15 = visit 2) with a subsequent 30-day follow-up period (to day 45).
The effectiveness of the therapy was assessed on the basis of objective symptoms (mucosal hyperemia and swelling of tonsils; investigator assessment at visits 1 and 2), subjective symptoms (achiness/fatigue, sore throat, pain in the extremities, headache, loss of appetite, cough, and hoarseness; parents rated and recorded the subjective symptoms in patient diaries) and responder rate. Further study parameters included time to symptom resolution, treatment compliance and concomitant medication intake. Adverse drug reactions were recorded to assess the tolerability.

Results: Patient distribution by age and gender was similar in both age groups (2–5; 6–11 years). The three most common inclusion diagnoses were nasopharyngitis, pharyngitis or tonsillitis. For these indications, the objective symptoms hyperemic mucosa and swollen tonsils nearly completely disappeared by visit 2 (range of relief: 93.4 % to 97.9 % of patients). Most subjective symptoms resolved within 4 days compared to 7 days in previous ARIs. Overall, a 3-day-shorter time to symptom resolution was achieved. 99.5 % of the patients were treatment responders, and 97 % tolerated the herbal medicine well or very well. Treatment compliance was very good (88.2 %).

Conclusions: Tonsilgon® N is a safe and effective treatment of acute upper respiratory tract infections in young children (aged 2–11 years) and is likely to reduce the duration of symptoms of ARI.

Keywords: Acute upper respiratory tract infections, Children, Effectiveness, Non-interventional study, Herbal medicine, Tolerability, Phytotherapy, Recurrent infections

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Background

Upper respiratory tract infections are a common occurrence in children. Such infections are a significant source of illness and pose a substantial economic burden on health services and society, in general [1]. Since most of these infections are of viral origin, usefulness of antibiotic therapy following recent guidelines on respiratory tract infections [2, 3] is not an option and overuse of antibiotic therapy must be avoided anyway. Plant-based medicines are a therapeutic option, especially because of their good tolerability. Since over 50 years now, the phytotherapeutic medicine, Tonsilgon® N (known as Imupret® N in some countries), is used worldwide to treat acute and recurrent infections of the respiratory tract [4]. Tonsilgon® N is an ethanolic-aqueous extract of seven medicinal plants, namely marshmallow root (*Althaeae radix*), chamomile flower (*Matricariae flos*), yarrow herb (*Millefolii herba*), oak bark (*Quercus cortex*), walnut leaves (*Juglandis folium*), horsetail herb (*Equiseti herba*), and dandelion herb (*Taraxaci herba*). These medicinal plants have established pharmacological effects including immune modulating, antiseptic, antibacterial, antiviral and anti-inflammatory properties [4, 5].

The respiratory epithelium represents a major portal of entry for pathogens. Complex defense mechanisms in this tissue prevent colonization and infection. In vitro studies with Tonsilgon® N on lung epithelial A549 cells point to a possible suppression of airway inflammation through inhibition of IL-8 and hBD-e production in epithelial cells [4]. In addition, Pahl described immunomodulatory effects of Tonsilgon® N on immune cells from healthy subjects in vitro [6], suggesting a favorable influence of Tonsilgon® N on the innate and adaptive immune systems. Furthermore, its effectiveness was discussed regarding the antioxidant defense system in children with chronic tonsillitis [7]. Clinical investigations in children so far comprised conservative and surgical treatment of acute and chronic upper respiratory tract diseases [8], the effectiveness and preventive action in children with frequent colds [9], as well as the treatment in viral respiratory infections [10, 11]. Moreover, Drynov and colleagues [12] studied Tonsilgon® N drops as prophylaxis for acute respiratory viral infections (ARVI) and recurrent chronic tonsillitis in children in Russia. A few years later, in 2008, Berger described the effectiveness and safety of Tonsilgon® N (drops and coated tablets) in children in the scope of an observational study carried out in Germany in 2006-2007 [5]. Therefore, experiences with Tonsilgon® N in the treatment of upper respiratory tract infections are generally very good [13, 14]. Despite the excellent clinical and immunological findings in these studies, and despite the fact that the use of this medicine is well known, it is a fact that the scientific literature contains few reports of its evidence-based effectiveness and safety in the treatment of acute upper respiratory tract infections (ARI).

In Russia, the approved indications for Tonsilgon® N are "acute and chronic diseases of the upper respiratory tract (tonsillitis, pharyngitis, laryngitis) and preventative treatment of complications in viral respiratory infections and as an adjunct to antibiotic therapy for bacterial infections." The aim of the present observational study was to demonstrate and document the effectiveness and safety of Tonsilgon® N in Russian children suffering from recurrent acute upper respiratory tract infections.

Methods

Study design

A prospective, non-interventional study (NIS) was carried out at 14 study sites (6 university teaching hospitals, 5 outpatient clinics and 3 private medical institutions) in Russia from March 2013 to February 2014. Included in the study were a total of 516 paediatric patients (boys and girls), aged 2–11 years ($N = 269$ in age group 2–5, 247 in age group 6–11, 2 out of range), with the diagnosis acute upper respiratory tract infections (ARI). The study was conducted following applicable GCP standards and in accordance with the Declaration of Helsinki in its most recent version. In addition, as per local practices, the study was approved by the local Independent Interdisciplinary Ethics Committee on Ethical Review for Clinical Studies and local ECs at those investigational sites where available. Parent(s) or legal guardians of each child provided written consent for the child's participation in the study. Clinical sites were monitored by clinical monitors of the contracted clinical research organization.

Inclusion criteria: children, aged 2–11 years; acute upper respiratory tract infections (ARI); physician's decision to carry out a therapy with Tonsilgon® N; Informed Consent (signed by parent(s) or legal guardian). The inclusion diagnoses were acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute tracheitis, acute laryngotracheitis, acute laryngopharyngitis with at least two ARI episodes in the last 6 months prior to visit 1 (enrolment); previous ARI episodes had to be documented in the patient source documents.

Exclusion criteria: no Informed Consent available; bacterial upper respiratory tract infection; antibiotic therapy at time of visit 1 (enrolment) or necessity for an antibiotic therapy; symptoms that were present since more than 3 days.

Study medication and dosage

Tonsilgon® N drops: 5-6 × 10 drops/day (for children aged 2–5 years) or 5-6 x 15 drops/day (for children aged 6–11 years) or Tonsilgon® N coated tablets: 5-6 × 1 coated tablets/day (for children aged 6–11 years)

Dosing Schedule: Treatment with the study medication for about 14 days (day 1 [visit 1] to about day 15 [visit 2]) followed by a follow-up phase lasting 30 days (to about day 45 [visit 3]) (see Fig. 1). Visit 1 was conducted on-site or as a phone call. Visit 2 took place on-site and visit 3 took place either on-site or by phone.

Study parameters

The key study parameters were the objective and subjective symptoms, time to resolution (sourced from recordings made by the parent(s)/legal guardian in the patient diaries), co-medication, adverse drug reactions (ADR) and global assessments of the effectiveness (responder rate) and tolerability.

Assessment of the effectiveness

Treatment effectiveness was derived from the two objective and seven subjective symptoms, with the change from visit 1 to visit 2. Objectively assessed symptoms were mucosal hyperemia and swelling of the tonsils, which were assessed by a physician. Subjectively assessed symptoms were achiness/fatigue, loss of appetite, sore throat, cough, headache, hoarseness, and pain in the extremities which were assessed by the parent(s)/patient. Symptoms were rated using the categories "none", "mild", "moderate", "severe" and "very severe".

Time to resolution: The time to symptom resolution (expressed in days) was established for each symptom on the basis of the recordings made in the patient diaries.

Responder vs. non-responder: Non-response was defined as the patient having one of the following:

- need for antibiotic treatment due to insufficient effectiveness of therapy including the study medication
- worsening of symptoms
- no change in symptoms.

Response was defined as "no need for antibiotic therapy and improvement in symptom course".

The number of responders was calculated.

Treatment compliance and co-medications

Dose intakes of study medication were noted in the patient diaries. Co-medications were also noted.

Tolerability assessments

The tolerability of the study medication was assessed on the basis of adverse drug reactions (ADR) recordings made by the physicians at visit 2 and visit 3 and through the recordings entered by the parents/legal guardians into the patient diaries.

Data and statistical analyses

This study was non-interventional and statistical hypothesis testing was not carried out. Descriptive statistics were applied and frequencies calculated. Moreover, in order to detect possible dependencies, a COX proportional hazard model with factors gender, age, compliance and drug formulation was calculated for the parameter 'time to resolution of symptoms'. SAS/STAT software (version 9.2) was used for the statistical analyses [15].

Results and discussion

The distribution of study patients and the acute upper respiratory tract infections in the 6 months preceding study enrolment is presented in Table 1. Initially, 518 paediatric patients were enrolled in the study, but 516 patients were included in the final analyses. One male patient proved to be a screening failure (only 1.8 years of age), and because there were no data available for this patient, he was excluded from the final analyses. One female patient was 12 years of age and so outside the per-protocol age limit. However, as there were data available for this patient, she was not included in the group of 6–11-year-olds but her data were listed separately.

The two patient groups—children aged 2–5 years and 6–11 years, respectively—showed a similar distribution in terms of the number of boys and girls in each of the age groups. Unfortunately, two children were inclusion failures so that in total 131 females (48.7 %) and 138

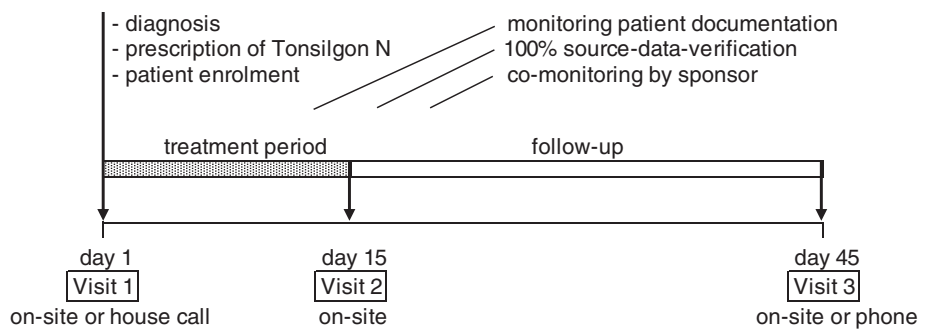

Fig. 1 Flow chart

Table 1 Distribution of patients and number of ARI in the last 6 months prior to enrolment

Age group	Gender	N	Number of acute upper respiratory tract infections					
			not recorded	once	twice	three times	four times	five times
2–5	female	131	2	1	95	27	4	2
	male	138			101	28	7	2
6–11	female	120			103	16	1	
	male	127			113	12	2	
	Total	516	2	1	412	83	14	4
	Total [%]	100.0	0.4	0.2	79.8	16.1	2.7	0.8

males (51.3 %) in the younger group (2–5 years) and 120 females (48.6 %) and 127 males (51.4 %) in the older group (6–11 years) of patients were evaluated. The younger group of children made up 52.1 % of the total study population, while the older group accounted for 47.9 % of the study population (see Table 1).

Regarding the number of previous ARI episodes that occurred in the 6 months leading up to study enrolment, most of the children experienced two episodes during this time, i.e. 79.8 % of the children, while 16.1 % of the patients experienced three ARI episodes. 3.5 % of the patients had even four or five episodes (see Table 1).

Protocol violations

There were a total of 96 major protocol violations. They were defined as follows (number of respective violations is cited here in brackets): violation of inclusion criteria: age > 11 years ($N = 1$), age < 2 years ($N = 1$); violation of exclusion criteria: intake of antibacterial drug at visit 1 ($N = 13$); patient had less than two episodes of acute respiratory viral infection in the 6 months preceding enrolment to the study ($N = 1$); non-compliant dosing regimens ($N = 55$), non-compliant concomitant medication ($N = 23$), or both ($N = 3$).

Moreover, there were two patients for whom the number of ARI prior to enrolment was not recorded. These two patients were enrolled, but withdrew consent directly afterwards, so that there were consequently no study data available for them.

As mentioned above, two patients did not meet the age related inclusion criterion. One patient was only 1.8 years old. There were no data for this patient and therefore the patient was not considered for evaluation. One further patient was 12 years of age, i.e. older than the maximal permitted age, and was therefore considered as another inclusion failure. For this female patient there were data available. It was decided to list her data, but to not include them in the analyses. In brief, she experienced two ARI episodes prior to enrolment, was diagnosed with an existing laryngotracheitis, her compliance was good and she was classified as a responder. Her objective symptoms (hyperemic mucosa, swollen tonsils) were moderate at visit 1 and were no longer present at visit 2. The subjective symptoms were mild (loss of appetite, cough, hoarseness and achiness/fatigue) at the beginning and completely gone at visit 2.

Analyses sets

The full analysis set (FAS) consisted of 516 patients (i.e. two less than the number of patients enrolled in the study). The per-protocol set (PPS) consisted of 422 patients, i.e. all patients without major protocol deviations. If not otherwise stated, the data presented in the tables and figures refer to the FAS.

ARI diagnoses at time of enrolment (visit 1)

The study patients were diagnosed with nasopharyngitis, pharyngitis, tonsillitis, laryngotracheitis, laryngopharyngitis, tracheitis, sinusitis and other (see Fig. 2) at the time of enrolment. Patients could have more than one

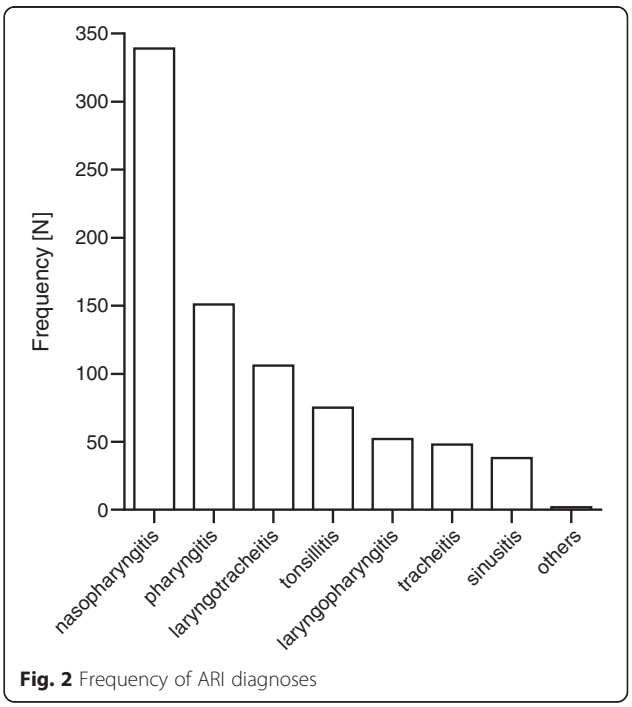

Fig. 2 Frequency of ARI diagnoses

diagnosis. The two age groups showed a similar distribution of ARI inclusion diagnoses (see Fig. 3).

Objective symptoms

Upon examination of the study patients, the investigators assessed the objective symptoms 'hyperemic mucosa' and 'swollen tonsils' at visit 1 and visit 2. At visit 1, 99 % of the study patients exhibited hyperemic mucosa and 83 % of the patients had swollen tonsils. The 14-day treatment achieved substantial relief of both these objective symptoms. No mucosal hyperemia was observed in 93 % of the patients at visit 2 and also tonsil swelling was, at this time, no longer present in 98 % of the children ($N = 516$ patients) following the Tonsilgon® N treatment (see Fig. 4). These findings provide a clear indication of the effectiveness of the herbal medicine.

Further review of the objective symptoms (swollen tonsils and hyperemic mucosa) at visit 1 and visit 2 shows a clear trend to substantial symptom relief for the patients with nasopharyngitis, pharyngitis or tonsillitis—the three most common indications present in this study. Both of the objective symptoms very much improved by visit 2 (see Table 2). For example, of the children suffering from nasopharyngitis and who had hyperemic mucosa at visit 1, $N = 339$ findings were rated predominantly as moderate and severe. 316 of these findings (93.2 %) were no longer present at the time of visit 2. The same is the case for swollen tonsils: At visit 1, 282 of 339 patients (83 %) had a mild, moderate, severe or very severe swelling of the tonsils. Then, at visit 2, 331 of these 339 findings (97.6 %) were reported as "none", i.e. as having resolved in the patients initially diagnosed with nasopharyngitis.

In the case of the patients with pharyngitis ($N = 151$), the objective symptoms hyperemic mucosa and swollen tonsils disappeared by visit 2 in the vast majority of cases. A total of 90.7 % ($N = 137$) of the finding hyperemic mucosa totally resolved by visit 2, while tonsil swelling disappeared in 98.7 % of the cases ($N = 149$).

Finally, the same trend occurs in the case of the patients diagnosed with tonsillitis ($N = 106$). Of the 106 findings of hyperemic mucosa (of mostly moderate severity) at visit 1, 91 (or i.e. 85.8 %) completely resolved by visit 2. Swollen tonsils ($N = 106$ patients at visit 1) almost disappeared completely after 14 days of treatment with the study medication ($N = 103$ or i.e. 97.2 %).

It can be summarized that for the three most common inclusion diagnoses nasopharyngitis, pharyngitis, and tonsillitis, the objective symptoms hyperemic mucosa and swollen tonsils nearly completely disappeared by visit 2. The extent of relief of these symptoms ranged from 93.2 % to 98.7 %.

Subjective symptoms

Here the parent(s)/legal guardians were called upon for their input regarding the subjective symptoms achiness/fatigue, loss of appetite, sore throat, cough, headache, hoarseness, and pain in the extremities. These symptoms and their severity were recorded in the patient diaries. The respective degrees of severity were described as "none", "mild", "moderate", "severe", and "very severe".

At visit 1, the subjective symptom experienced by the most patients (approx. 89 %) was achiness/fatigue (see Fig. 5). This symptom occurred at all levels of severity, followed closely by loss of appetite (approx. 86 %) and sore throat (approx. 85 %). Cough was experienced slightly less frequently, with ratings of mild, moderate, severe, and very severe reported by the parents in around 79 % of the cases. Headache was predominantly mild and moderate in severity, with just around 4 % of

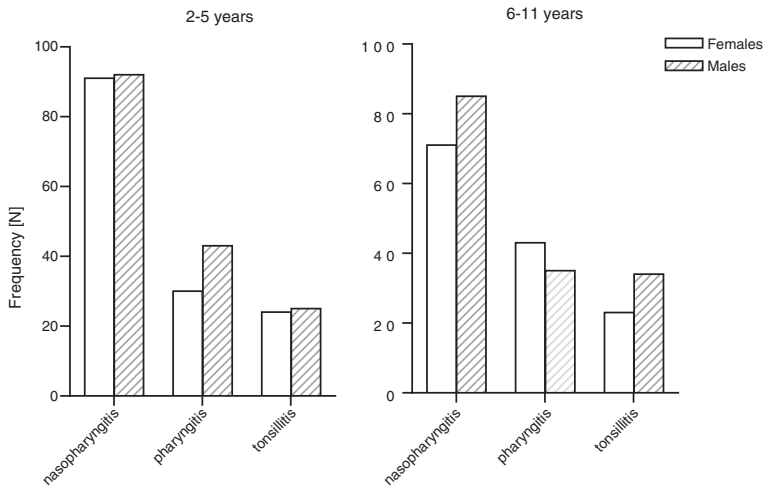

Fig. 3 Frequency of the three major ARI diagnoses by age group and gender

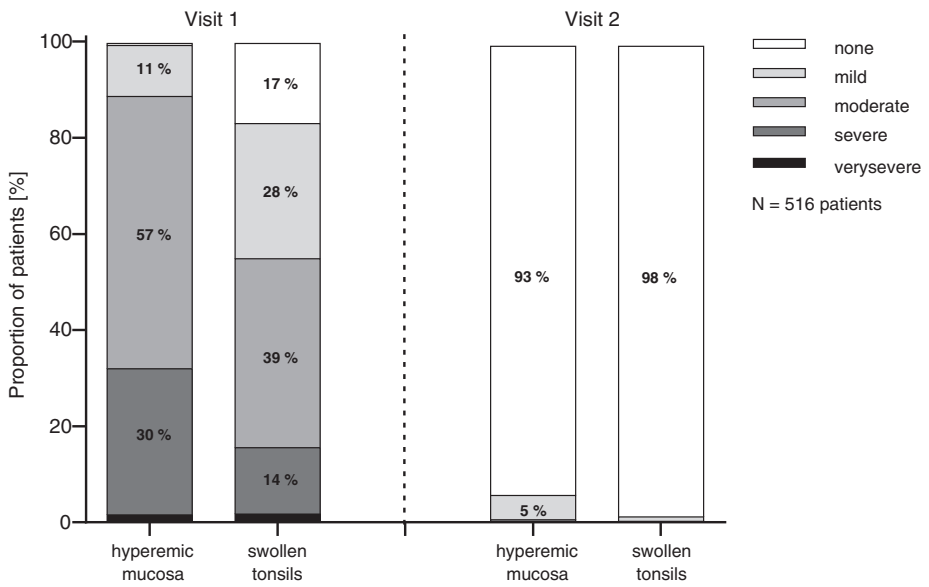

Fig. 4 Objective symptoms. Proportion of patients by degree of symptom severity and visit

the patients experiencing severe or very severe headache. Overall, this subjective symptom was reported for less than 60 % of the patients. The least frequent subjective symptoms reported were hoarseness (around 25 %) and pain in the extremities in around 21 % of the patients. The severity of these two subjective symptoms was rated as being mild, moderate, severe, and very severe, although only around 1.4–3.3 % of the patients complained of severe and very severe hoarseness and pain in the extremities (see Fig. 5).

After 14 days of treatment with the study medication when the patients were examined again at visit 2, there was a dramatic drop in the proportion of patients experiencing subjective symptoms (Fig. 5). All of the symptoms had nearly disappeared. Only a very small proportion of patients still had mild achiness/fatigue and sore throat (0.78 % each), loss of appetite (approx. 3 %), cough (mild and moderate severity reported in approx. 3 % of the patients) and hoarseness (mild and moderate severity; around 0.4 %). Lastly, for all intents and purposes, headache and pain in the extremities completely disappeared in all 516 patients (FAS) by visit 2.

Time to resolution

The assessment of the 'time to resolution' was based on diary entries of the patients/parent(s). As there was no continuous observation accompanied by a medical assessment between visit 1 and visit 2, the assessment reflects rather the impression of patients/parent(s) and should not be over-interpreted. Since the duration of former diseases was assessed retrospectively, these assessments should be handled with care.

The patients' medical history showed that the mean time to resolution of the previous ARIs was 7.65 days (median: 7 days), irrespective of age or gender. Based on information in the patient diaries, the majority of subjective symptoms resolved within 4 days (median) compared to 7 days in previous ARIs. The exceptions here are the subjective symptoms cough (median time to resolution = 6 days) and headache (median time to resolution = 3 days). Data of the time to resolution of the subjective symptoms underwent a multivariate statistical analysis using the COX proportional hazard model which took into account the factors gender, age, compliance, and drug formulation. The factors rarely affected the time of resolution—an exception was 'pain in the extremities' which was associated with gender ($p = 0.0363$; i.e. the symptom lasted longer in boys). Moreover, the time to resolution of cough ($p = 0.0038$) and loss of appetite ($p = 0.0024$) was age-related: The older the child was, the longer it took for these symptoms to resolve.

Treatment compliance

In this non-interventional study, it was possible to observe treatment compliance under realistic conditions. Of the total 516 patients of the FAS, 455 or i.e. 88.2 % were compliant. Six patients had no treatment compliance data available (see Table 3). In the case of 55 patients, the reasons for which they were considered non-compliant were that either the drug dose had been changed, or the drug intake was irregular or both—i.e. the drug dose was changed and the intake of the study medication was irregular. There were slightly more cases of non-compliance noted for the younger group of

Table 2 Objective symptom severity at Visit 1 and Visit 2

		findings [N]		visit 2					
		visit 1		none	mild	moderate	severe	very severe	missing
nasopharyngitis	hyperemic mucosa	none	1	1					
		mild	37	36	1				
		moderate	203	193	6	1	1		2
		severe	97	85	10	1			1
		very severe	1	1					
		missing							
		total	339	316	17	2	1		3
	swollen tonsils	none	57	57					
		mild	100	98	1				1
		moderate	132	128	2	1			1
		severe	47	45	1				1
		very severe	3	3					
		missing							
		total	339	331	4	1			3
pharyngitis	hyperemic mucosa	none							
		mild	8	7	1				
		moderate	76	68	6	1	1		
		severe	62	57	5				
		very severe	5	5					
		missing							
		total	151	137	12	1	1		
	swollen tonsils	none	18	18					
		mild	39	38	1				
		moderate	59	58		1			
		severe	31	31					
		very severe	4	4					
		missing							
		total	151	149	1	1			
tonsillitis	hyperemic mucosa	none							
		mild	12	11	1				
		moderate	67	59	6	1	1		
		severe	25	19	6				
		very severe	2	2					
		missing							
		total	106	91	13	1	1		
	swollen tonsils	none	1	1					
		mild	36	35	1				
		moderate	53	51	1	1			
		severe	15	15					
		very severe	1	1					
		missing							
		total	106	103	2	1			

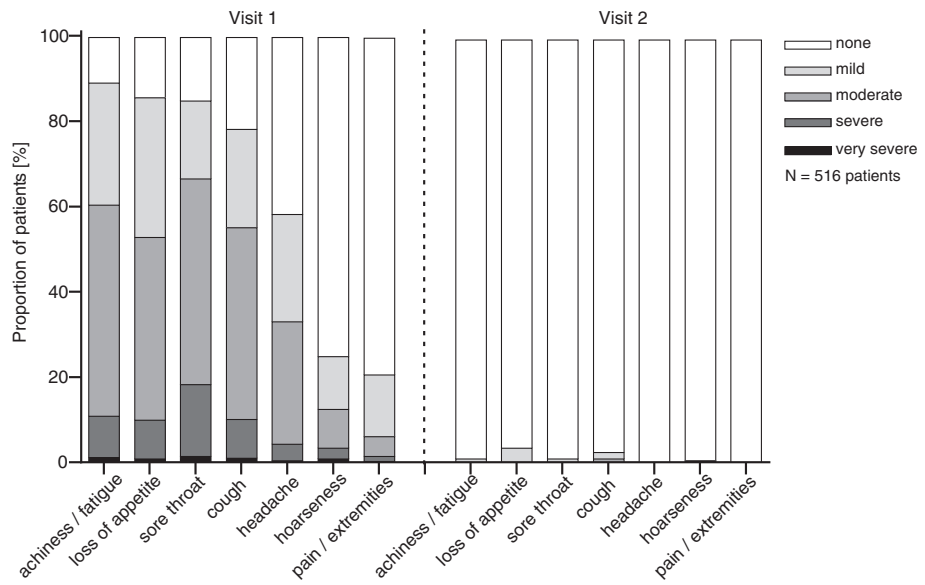

Fig. 5 Subjective symptoms. Proportion of patients by degree of symptom severity and visit

patients (2–5 years of age). Of the 55 non-compliant patients, 29 were in the younger group (2–5 years) and 26 were in the older group of patients (6–11 years). Despite the non-compliance in 10.7 % of the total 516 cases, by far the overall majority of patients were compliant. With a treatment compliance rate of 88.2 %, one can summarize that the overall treatment compliance in this study was very good. Moreover, it cannot be ruled out, that as symptoms improved, the parent(s) decided to reduce the dosing frequency to 3 times daily, as recommended in the package insert. Therefore, it may be assumed that the 'actual patient compliance' was even higher.

Concomitant medication

Concomitant medications according to the WHO/DDD classification had to be recorded by the investigator and parent(s)/legal guardians (in the patient diaries).

Parallel to the study medication, the types of concomitant medications most reported were preparations for the respiratory system, e.g. antihistamines, nasal and throat preparations, drugs for obstructive airway disease and cough and cold remedies.

Assessment of global effectiveness

Responder rates

A "responder" was defined as a patient in whom the symptoms resolved completely or were relieved. In the case of "non-responders", the patient's symptoms did not change, worsened or the patient required antibiotic therapy. Based on these definitions, nearly all of the patients (99.5 %) of the PPS—irrespective of age or gender—were classified as "responders" (see Table 4). Two patients, who received drops, did not respond to the phytotherapy. One patient had no change in his/her symptoms and four patients needed antibiotics.

Tolerability assessment

Analysis of the results of the global tolerability assessments by the investigators and patients/parents revealed that the treatment was well-tolerated (tolerability rating of "good") or very well-tolerated (tolerability rating of

Table 3 Treatment compliance

		Compliance			Reasons for non-compliance		
Age group	Gender	yes	no	not recorded	drug dose changed	irregular drug intake	drug dose changed and irregular intake
2–5	female	113	13	5	13	4	
	male	121	16	1	12		
6–11	female	111	9		7		2
	male	110	17		16	1	
Total	516	455	55	6	48	5	2
Total [%]	100.0	88.2	10.7	1.2	9.3	1.0	0.4

Table 4 Responders

PPS (*N* = 422)	Responder N	Non-Responder N	Total N	Responder [%]
Total	420	2	422	99.5
Age group 2–5	204	2	206	99.0
Age group 6–11	216		216	100.0
Females	210	1	211	99.5
Males	210	1	211	99.5

"very good") in the vast majority of cases—for both the FAS and PPS (see Table 5). These ratings were given by both the investigators and the patients/parents. In total, no serious ADR and only one non-serious ADR occurred in one patient in the form of urticaria on the extremities. It turned out that this patient had a known history of allergy to Matricaria. The treatment was withdrawn and no further measures were required. The patient recovered completely. Moreover, allergy against the compositae plant family is a known contraindication of Tonsilgon® N and is stated as such in the package insert.

In summary, Tonsilgon® N (Imupret® N) is a well-known traditionally used herbal medicine for the treatment of upper respiratory tract infections. Our findings mirror many of those reported in the literature. For example, as reported by Drynov and colleagues [12], Tonsilgon® N was effective for the treatment of acute respiratory viral infection and chronic recurrent tonsillitis in 32 paediatric patients, aged 3–15 years. A 6-month treatment with the liquid drug presentation (drops) resulted in substantial symptom improvement even 1 year after treatment start. In addition, these authors showed a good correlation between the clinical findings and the patients' IgG values.

Further proof of effectiveness and tolerability of the herbal preparation is clear from the results obtained in the 2006-2007 German observational study of Tonsilgon® N in children with acute respiratory infections [5]. Our findings confirm those reported by Berger, who demonstrated the medication's effectiveness and safety in over 1100 children, aged 2–17 years, with recurring upper respiratory tract infections. Berger also described the immunomodulatory and antibacterial properties of the herbal combination preparation as well as its usefulness in relieving symptoms of inflammation.

Table 5 Tolerability assessment

	FAS (*N* = 516 [a])				PPS (*N* = 422)			
	Patient/parents		Investigator		Patient/parents		Investigator	
	N	%	N	%	N	%	N	%
poor	1	0.2	1	0.2	0	0.0	0	0.0
moderate	2	0.4	13	2.5	1	0.2	9	2.1
good	262	50.8	262	50.8	227	53.8	223	52.8
very good	246	47.7	235	45.5	194	46.0	190	45.0

[a] *N* = 5 not recorded

In the present study, treatment with Tonsilgon® N achieved nearly complete resolution of symptoms and a 3-day-shorter duration of the illness compared to the course of preceding ARIs, according to the entries about previous ARIs in patient medical documents. The study medication was also well-tolerated and it may be noted that the availability of the medicine in coated tablet form as well as in a liquid presentation (drops) makes dosing easy and convenient for young patients.

Conclusions

It can be concluded that the herbal combination medicine, Tonsilgon® N, is a safe and effective treatment of acute upper respiratory tract infections in young children (aged 2–11 years) and is likely to reduce the duration of symptoms of ARI. Such clinical outcome benefits not only the patients and their families, but indeed may also relieve the time and financial burden on health care services.

Abbreviations

ADR: Adverse drug reaction; ARI: Acute upper respiratory tract infections; ARVI: Acute respiratory viral infections; FAS: Full analysis set; NIS: Non-interventional study; PPS: Per-protocol set; WHO/DDD: World Health Organization/defined daily dose.

Competing interests

D. Abramov-Sommariva, H. Steindl and M. Wonnemann are employees of Bionorica SE, Germany. I. Kolchenko is an employee of Bionorica LLC, Russia. All other authors and investigators of the study do not have any conflict of interest.

Authors' contributions

VV has made substantial contributions to the conduct of the presented study, acquisition and interpretation of data. DAS has been substantially involved in the interpretation of data and has given final approval of the version to be published. HS has made substantial contributions to conception and design of the study, acquisition of data, and analysis and interpretation of data. MW has been involved in drafting the manuscript, revising it critically for important intellectual content, ensuring that questions related to the accuracy or integrity of the work are resolved. EGR has made substantial contributions to the conduct of the presented study and acquisition of data. TVR has made substantial contributions to the conduct of the presented study and acquisition of data. AAL has made substantial contributions to the conduct of the presented study and acquisition of data. IIK has made substantial contributions to conception, design, and to the management of the study, and has been involved in drafting the manuscript, revising it critically for important intellectual content. All authors read and approved the final manuscript.

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