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Rhinology

A prospective study on the efficacy of dupilumab in chronic rhinosinusitis with type 2 inflammation

Studio prospettico sull'efficacia di dupilumab per rinosinusite cronica con infiammazione di tipo 2

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SUMMARY

Objective. Treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) includes endoscopic sinus surgery and topic and/or systemic corticosteroids, which have only temporary effects. The development of biologic therapies has provided a new treatment paradigm for CRSwNP. Dupilumab is the only biological approved in Italy for CRSwNP, but its efficacy in a real-life context is still scarce.

Methods. We carried out a monocentric prospective study at our institution with a 6-month follow-up on patients administered biweekly 300 mg dupilumab therapy for CRSwNP, prescribed according to EPOS 2020 criteria. Patients were evaluated at baseline and every 2 months.

Results. Median values at baseline and 6 months were, respectively, 3/12 and 8/12 for the Brief Smell Identification Test ($p = 0.005$), 5/8 and 2/8 for the Nasal Polyp Score ($p < 0.001$), 10/20 and 6/20 for the Lund-Kennedy score ($p < 0.001$), 65/110 and 14/110 for the Sinonasal Outcome Test ($p < 0.001$), and 15/25 and 23/25 for the Asthma Control Test score ($p = 0.009$). Adverse events were mild, consisting mainly in discomfort at the site of injection. Four patients developed asymptomatic hypereosinophilia. The treatment was not discontinued in any patient.

Conclusions. Dupilumab was confirmed to be an effective and safe treatment for CRSwNP, as previously seen in registrational studies.

KEY WORDS: chronic rhinosinusitis with nasal polyps, biological therapy, monoclonal antibody

RIASSUNTO

Obiettivi. *Il trattamento della rinosinusite cronica include la chirurgia nasosinusale endoscopica e la terapia steroidea locale e sistemica. I nuovi farmaci biologici hanno fornito un efficace strumento contro i sintomi della malattia. Dupilumab è l'unico biologico approvato in Italia, ma l'evidenza circa la sua efficacia nella pratica clinica è limitata.*

Metodi. *Questo articolo riporta uno studio prospettico monocentrico su pazienti in follow up per 6 mesi durante la terapia bisettimanale con dupilumab, secondo i criteri proposti da EPOS2020. I pazienti sono stati valutati prima della terapia e ogni due mesi.*

Risultati. *I valori mediani prima della terapia e a 6 mesi mostrano un miglioramento nell'olfatto, misurato mediante un test oggettivo (Brief Smell Identification Test), nella dimensione dei polipi, nell'infiammazione della mucosa nasale, nella qualità di vita dei pazienti e nel controllo dell'asma. Gli effetti collaterali sono stati di lieve entità: il più comune è stato il dolore in sede di iniezione. 4 pazienti hanno sviluppato un'ipereosinofilia asintomatica. Il trattamento non è stato interrotto in nessuno di questi casi.*

Conclusioni. *Nella nostra esperienza, il trattamento con dupilumab è stato efficace e sicuro in linea con i risultati degli studi di registrazione.*

PAROLE CHIAVE: *rinosinusite cronica polipoide, terapia biologica, anticorpi monoclonali*

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Introduction

Chronic rhinosinusitis (CRS) is a common condition which has a serious impact on healthcare systems [1]. Traditionally it has been divided, depending on its phenotype, into chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP). This latter condition, representing around 25-30% of cases, is associated with significantly higher morbidity and worse quality of life [2,3]. More recently, the increasing evidence on the aetiopathogenetic mechanisms underlying CRS has led to a shift of paradigm towards a classification based on the endotype of the CRS, as reflected by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) in 2020 [4]. Studies relating endo- and phenotype have shown that CRSwNP is more commonly associated, especially in European and North American patients, with a pattern of type 2 inflammation; this type of inflammation, whose major markers are interleukin (IL)-4, IL-5 and IL-13, is determined by a complex cooperation between eosinophils, mast cells and innate lymphoid cells [5]. Unfortunately, the therapeutic armamentarium against CRSwNP has long been completely unsatisfying: traditionally, corticosteroids are the only molecules that can halt the type 2 inflammatory cascade and intranasal corticosteroids (INCS) are sufficient in only a proportion of cases, while systemic therapy is burdened by serious side effects and therefore limited in time. As a consequence, for patients whose disease status was not controlled by nasal sprays, the ENT surgeon is often challenged to find a difficult balance between frequent revision surgeries, courses of systemic corticosteroids and the need to prevent short- and long-term risks [1].

In this context, the recent introduction of monoclonal antibodies, also known as biological therapies, represents a turning point for the treatment of CRSwNP. These drugs specifically target inflammatory mediators or immune cells, and have been shown to be effective not only in severe asthma and atopic dermatitis (AD), but also in CRSwNP. Even though additional molecules are expected to be approved soon, dupilumab is the only biologic therapy that can be currently prescribed in Italy for CRSwNP, since January 2021. This molecule is a fully human, VelocImmune-derived IgG-4 monoclonal antibody, that inhibits the activity of the shared receptor subunit of IL-4 and IL-13, thus blocking signalling from both. Although its efficacy and safety have been extensively investigated in two major multicentre, randomised, double-blind, placebo-controlled, phase 3 trials (SINUS24 and SINUS52), reports of its use outside the framework of a clinical trial are scarce [6,7].

The current study investigated the experience of our centre in the treatment of patients suffering from CRSwNP during the first year after approval of dupilumab in Italy. This represents an early description of its use in real-life experience, also depicting our approach to preliminary screening and evaluation, as well as subsequent monitoring of the disease.

Materials and methods

Study design and endpoints

This is a prospective, observational, cohort, monocentric study assessing the effectiveness and safety of dupilumab in patients with CRSwNP. All patients who were prescribed dupilumab for CRSwNP and who were followed for at least 6 months in our hospital were included. All patients were prescribed dupilumab according to EPOS 2020 criteria, i.e. presented bilateral polyposis, underwent at least one previous endoscopic sinus surgery (ESS) and presented at least 3 of the following 5 criteria: evidence of Th2 inflammation (tissue eosinophilia > 10/hpf OR blood eosinophilia ≥ 250 OR total IgE ≥ 100), need for systemic corticosteroids (≥ 2 courses per year OR ≥ 3 months of low dose systemic corticosteroids) or contraindication to steroids, significantly impaired quality of life (SNOT-22 ≥ 40), significant loss of smell (anosmic on smell test), diagnosis of comorbid asthma (asthma needing inhaling corticosteroids) [4].

All patients underwent preliminary blood tests, measuring basal cell blood count (CBC), levels of serum IgG, IgA, IgM, IgE, C-reactive protein (CPR), and anti-nucleus (ANA) and anti-neutrophil cytoplasmic antibodies (cANCA and pANCA) to rule out immunodeficient or autoimmune conditions, such as eosinophilic granulomatosis with polyangiitis. Patients suffering from asthma were evaluated by an allergist or pneumologist, and none of the patients met the requirements for the prescription of a doubled primary dose.

If the abovementioned screening was permissive, a multidisciplinary team of ENT surgeons and allergists met and eventually prescribed dupilumab 300 mg subcutaneously every two weeks for CRSwNP. The baseline visit investigated the following parameters:

- past medical history: a) presence of comorbidity, with particular attention to asthma and AD; b) presence of allergies or intolerance to acetylsalicylic acid (ASA) or to other non-steroidal anti-inflammatory drugs (NSAIDs); c) number of EPOS 2020 criteria met (ranging from 3 to 5) [4]; d) date of previous surgery/ies;
- quality of life assessment: a) Sino-Nasal Outcome Test-22 (SNOT-22), (range 0-110) [8]; b) Brief-Smell Identification Test (B-SIT), (range 0-12): olfactory function was considered normal if ≥ 9, hyposmia corresponds to 5-8 and anosmia to ≤ 4 [9]; c) Olfaction Visual Analogue

Scale (VAS), (range 0-10); d) in asthmatic patients, the Asthma Control Test (ACT) was used (range 5-25) [10];
- endoscopic findings, obtained with a 0°/30° rigid nasal endoscope: a) NPS (Nasal Polyp Score) (range 0-8); b) Lund-Kennedy score (LKS) (range 0-20) [11]. We used two different endoscopic scores because NPS mainly focuses on the dimension of polyps, while LKS provides additional information on mucosal oedema and nasal secretion and, in general, on the grade of inflammation;
- radiological findings on the last CT: a) Lund-Mackay score (LMS) [12]; b) ACCESS score [13]. Both scores vary from 0 to 24. CT scans were obtained after the last surgery and as close to the first administration as possible, with a median of 2 months between the CT scan and the first dose.

Patients were advised not to discontinue nasal douches and intranasal corticosteroids (INCS) (as their therapy for asthma, if any) and, immediately after the baseline visit, the first injection was administered subcutaneously in the presence of the ENT surgeon to instruct the patient on self-administration and recognise possible side effects related to the first dose. Subsequent injections were performed by the patients themselves at home.

The scheduled follow-up included a visit every two months for six months. During these visits, the ENT surgeon reevaluated the abovementioned parameters at endoscopic examination, and the questionnaires on quality of life and the olfactory tests were submitted again. In addition, patients were asked to undergo new blood tests, including CBC, total IgE, and CPR, every two months from baseline. Side effects and compliance with therapy were recorded. At 4 and 6 months response to biological treatment was evaluated according to EPOS 2020 criteria, counting how many of the following five criteria were met: reduced nasal polyps size, reduced need for systemic corticosteroids, increased quality of life, improved sense of smell and reduced impact of comorbidities [4].

Statistical analysis

Data are reported as median and interquartile range (IQR). Comparison between times was evaluated by Wilcoxon signed rank test with Bonferroni Correction and statistical significance was considered for $p < 0.05$. Computations was done with R 4.1.3.

Results

A total of 21 patients with a median age of 47 years (range 29-84) completed the 6-month follow-up (FU) (16 M, 5 F). All patients had undergone previous endoscopic sinus surgery (ESS) with a median of 2 previous endoscopic surgical procedures (range 1-7); in the 19 cases in which a CT scan was performed after the last surgery and the subsequent recurrence of symptoms was available, the median values of the Lund-Mackay and ACCESS scores were 21 (18-23) and 10 (4-15), respectively. Altogether, 15/21 (71%) patients in the cohort suffered from asthma.

In 9 cases, asthma was associated with ASA sensitivity, with the subsequent presence of the triad for diagnosis of NSAIDs-exacerbated respiratory disease (N-ERD). The results are reported in Table I.

The blood tests did not result in any first diagnosis of latent rheumatologic disease or any abnormality determining a contraindication to biologic treatment. Subcutaneous self-administration was considered easy to perform by all patients; only in a single administration was loss of the drug reported.

All examinations, tests and questionnaires showed progressive and significant improvement compared to baseline (p-values are shown in Table II). The median SNOT-22 at baseline and at 2, 4 and 6 months was 65, 23, 24 and 14, respectively (Fig. 1); in the same time intervals, endoscopic examinations revealed a median for NPS of 5, 3, 2 and 2 and for Lund-Kennedy of 10, 8, 6 and 6 (Fig. 2). Olfactory performance evaluated with B-sit was poor at baseline with a median of 3/12, but reached 8/12 at the end of follow-up (interim values of 6/12 and 8/12 at 2 and 4 months), (Fig. 1); these results were comparable with the subjective data obtained with olfactory VAS, showing a median of 0, 6, 7 and 8 at the consecutive intervals. Analogously, the ACT score displayed a progressive increase (15/25, 21/25, 22/25, 23/25), thereby depicting improvement in asthma control. The abovemen-

Table I. Variables at baseline. Age, eosinophil absolute count, total IgE, Lund-Mackay score, ACCESS score and number of previous surgeries are indicated as median values and in parentheses the minimum and maximum value. For sex, the number of male (M) and female (F) patients is indicated. For asthma and N-ERD, the total of patients of the 21 included with specific comorbidity are listed.

Variable (n = 21)	Values
Age	47 (29-84)
Sex	16 M, 5 F
Presence of asthma	15/21
NSAIDs-exacerbated respiratory disease (N-ERD)	9/21
Eosinophil absolute count (EAC)	0,54 (0-1,1)
Total IgE	69 (31-643)
Lund-Mackay score	21 (18-23)
ACCESS score	10 (4-15)
Number of previous surgeries	2 (1-7)

Table II. Median value and interquartile range of the main variables at baseline and at 2, 4 and 6 months. The p-value refers to the comparison versus baseline with Wilcoxon signed rank test and Bonferroni correction. Data are reported as median and interquartile range. ACT was applicable in 15/21 patients.

Variable (n = 21)	Baseline	2 months	4 months	6 months
SNOT-22 median [IQR] (0-120)	65 [48, 74]	23 [19, 42] (p < 0.001)	24 [9, 33] (p < 0.001)	14 [5, 28] (p < 0.001)
NPS median [IQR] (0-8)	5 [5, 6]	3 [2, 4] (p < 0.001)	2 [2, 4] (p < 0.001)	2 [0, 3] (p < 0.001)
Lund-Kennedy score median [IQR] (0-20)	10 [8, 10]	8 [6, 8] (p = 0.016)	6 [6, 8] (p = 0.009)	6 [4, 6] (p < 0.001)
B-SIT median [IQR] (0-12)	3 [3, 5]	6 [4, 8] (p = 0.030)	8 [5.50, 9] (p = 0.009)	8 [6.75, 9.25] (p = 0.005)
VAS olfaction median [IQR] (0-10)	0	6 [3, 7] (p < 0.001)	7 [5, 8] (p < 0.001)	8 [7, 9] (p < 0.001)
ACT score median [IQR] (5-25)	15 [10.75, 19.25]	21 [19.75, 22.25] (p = 0.003)	22 [20, 24] (p = 0.007)	23 [21.50, 24] (p = 0.009)

SNOT-22: SinoNasal Outcome Test-22; NPS: Nasal Polyp Score; B-SIT: Brief-Smell Identification Test; VAS: Visual Analog Scale; ACT: Asthma control Tes; IQR: InterQuartile Range.

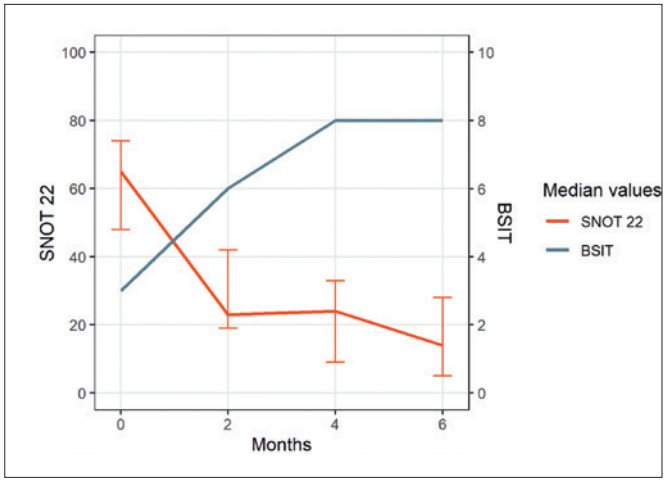

Figure 1. Median values of Sino-Nasal Outcome Test-22 (SNOT 22) and Brief Smell Identification Test (BSIT) during the study.

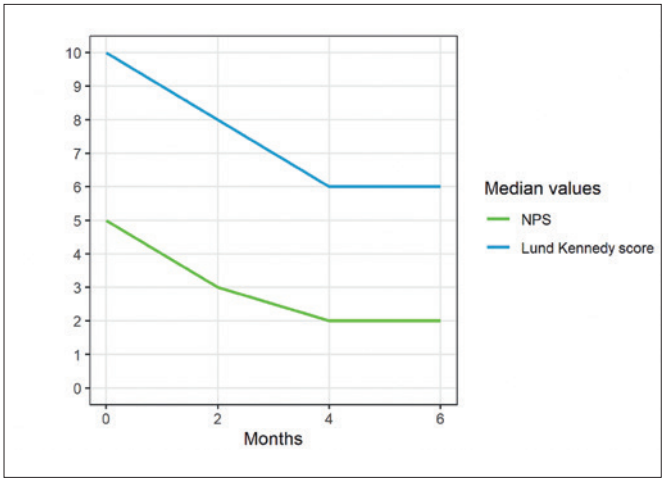

Figure 2. Median values of endoscopic findings for Nasal Polyp Score (NPS) and Lund-Kennedy score during the study.

tioned results and the corresponding IQRs are shown in Table II. Despite being instructed to continue their previous therapy, 8 patients admitted to having suspended mometasone spray and 4 suspended asthma therapy for a period during follow-up, mainly due to the perceived lack of need consequent to their improved condition. There were no acute exacerbations of symptoms requiring oral corticosteroids.

The EPOS 2020 criteria met for the prescription of therapy had a median of 4/5, while the median at 4 and 6 months of the criteria met for defining response to biological treatment was 5/5. Only one patient had a poor response, i.e. ≤ 2 criteria of 5, with stable NPS and LMS, no improvement in olfaction, no impact on its comorbidities (the patient was not affected by asthma), and a 9-point reduction in SNOT-22.

The adverse events seen were mainly mild, consisting of discomfort or burning at the site of injection or transient weakness/headache. One patient reported conjunctivitis treated with topical therapy, while another underwent a course of antibiotics due to a purulent discharge from the nose; one patient reported the development of wheals after drug administration at 3-4 months of therapy, with spontaneous resolution.

As already known from the registration studies, an increase in eosinophil absolute count (EAC) was observed. EAC at baseline, 2, 4 and 6 months had a median of, respectively, 0.50, 0.90, 0.85 and 0.80. Similarly, total IgE had a median of 128.00, 77.60, 63.90 and 57.75 [22.58, 93.85]. In four cases, EAC reached values for hypereosinophilia (> 1.5 x 10^9/L): in those cases, we repeated blood tests every month instead of every two months. None showed any symptoms related to hypereosinophilia, but in two cases patients were preventively treated with a short-term course of corticosteroids as EAC reached values > 3 x 10^9. In those two cases, we performed routine blood tests to assess liver, heart and renal function, which showed no signs of organ involvement. The management of dupilumab-induced hypereosinophilia is thoroughly described in our previous publication [14].

Discussion

A new era in the treatment of type 2 inflammation has begun with the introduction of biological therapy in clinical practice [15]. Dupilumab, the first molecule receiving approval for CRSwNP, showed promising results during registrational studies with a low number of adverse events [6]; evidence from real-life practice is scarce [7,16,17]. To our knowledge, this is one of the first studies reporting on outcomes of dupilumab prescribed for CRSwNP in a real-life context.

The present analysis confirms the efficacy of dupilumab in reducing NPS and improving quality of life, sense of smell and control of asthmatic comorbidity, as well as a low number of side effects. The time to onset is rapid, with a significant reduction at 2 months of 2 and 42 points for median NPS and SNOT-22, respectively; the subsequent months show further progressive improvement, although less pronounced. Similar considerations apply to olfactory function for both objective (B-SIT) and subjective (olfactory VAS) assessments: at 4 months, the median B-SIT values rose from anosmia (3/12) to the superior limit of hyposmia (8/12), as olfactory function is considered normal if ≥ 9/12, and the median VAS from 3 to 7. It is worth specifying that previous studies have suggested that the olfactory dysfunction in CRSwNP is not attributable only to the conductive obstruction to the olfactory cleft, but also due to a complex mechanism related to type 2 inflammation, which alters the concentration of olfactory mucus, inhibits the olfactory neural regeneration and leads to olfactory bulb atrophy as a consequence of prolonged loss of stimuli [18]. As biologics determine both polyp shrinkage and a reduction in inflammatory neurotoxins, their action on olfactory function is multifactorial [18]; further studies are needed to assess the role of therapy in the olfactory epithelium renewal after disuse atrophy and/or surgical harm.

Nevertheless, predisposition to type 2 inflammation is a systemic condition that implies multidisciplinary evaluation to assess type 2 comorbidities [4,19]. Among these, particular attention should be paid to the eventual tapering of corticosteroid (CS) therapy for asthma or AD: previous reports suggest that the reduction of topical steroids in AD may play a role in the transient increase in AEC observed during dupilumab treatment, although it has been mainly ascribed to the inhibition of eosinophilic chemotaxis [20]. Multidisciplinary evaluation may therefore postpone CS tapering in patients with high AEC until normalisation of the blood count. For the same reason, counseling should emphasise the need for adherence to therapy: even if advised differently, a considerable proportion of our patients stopped or tapered their therapy for CRSwNP or asthma as it was no longer considered necessary.

If on the one hand, our study is consistent with the present literature on the efficacy and safety of dupilumab, on the other hand major concerns about its cost have arisen [17,21]. A recent article by Scangas et al. took a position against biologic therapy in comparison to ESS for primary therapy when taking into account quality-adjusted life-year (QALY); but also reported that revision ESS is more cost-effective in case of recurrent polyposis [1]. However, as the authors explicitly state in the article, the analysis is biased by the possible effects of multiple anaesthesias and the increasing surgical difficulty in revision ESS, which are not easily quantifiable [21]. Regarding the economical sustainability of biological therapy, future studies should address two main issues: the optimal interval for administration and the patients who could benefit most from it. In relation to the first point, our results confirm that the improvement in symptoms and reduction in polyp size is rapid. It might be possible to consider, after reaching an adequate control of nasal polyps, to progressively prolong the interval between doses: registrational studies, in fact, supported a two-week interval administration (Q2W) for its superior efficacy, but data from SINUS 52 may suggest that a monthly regimen might be sufficient as a maintenance dose after adequate response [6]. This option has been already tested in AD [22,23], and a pioneering contribution on CRSwNP has been provided by the study by Van Der Lans et al., who investigated a stepwise interdose interval prolongation until Q6W in patients with moderate to excellent response with satisfying results [7].

A second topic worthy of further exploration is identification of a subset of patients who may benefit more from biologics, thereby increasing the cost-efficacy ratio [24]. In this perspective, it must be considered that dupilumab inhibits type 2 inflammation, which (in Western countries) is responsible for a majority – but not all – cases of CRSwNP; nevertheless, the evidence of this kind of inflammation is not strictly mandatory for prescription. In this regard, the patient in the present study who had the poorest response to therapy in the 6-month period (only 9-point reduction in SNOT-22, stable NPS and LKS, only 2 criteria for response according to EPOS2020) had laboratory tests that were not suggestive of type 2 inflammation at baseline. A similar finding, in fact, has been reported by Van Der Lans et al. [7], and some guidelines already consider the evidence of type 2 inflammation as a mandatory requirement for biologic therapy [19,25].

Our study has some limitations: first, some data is missing due to its prospective design; moreover, spirometry was required only in patients suspected for insufficient control of disease, while other asthmatic subjects were investigated through the ACT score. Lastly, we included a relatively low

sample size, due to the monocentric design of the study, and therefore no sub-analysis was possible. On the other hand, the monocentric design guarantees uniform management of patients, and more consistence in assigning endoscopic scores.

Despite these limitations, this paper represents one of the first descriptions of the use of dupilumab in CRSwNP in real-life practice; the clinical condition of patients was examined through several tests, and the prospective nature of the study supports the reliability of our data.

Conclusions

Our study confirms the efficacy and safety of dupilumab reported in registrational studies in a real-life context for all the main assessment parameters of CRSwNP. Its prospective design is responsible for the high reliability of its results, which, combined with those from previous studies, stimulate discussion for future perspectives. In particular, confirmation of the efficacy of dupilumab with interdose interval prolongation and better definition of patients eligible for therapy is a challenge for future studies.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AV, AR, UT and AN made substantial contributions to conception, design and acquisition of data, drafted the article and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; MT, MRY and MB made substantial contributions to conception of the data, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical consideration

Informed consent was obtained from each patient for treatment and use of de-identified clinical data for study purposes; the study was approved by the institutional review board (IRB) of San Raffaele Hospital (Comitato Etico Ospedale San Raffaele, 112/INT/2021), and conducted according to the ethical standards established in the 1964 Declaration of Helsinki, as revised in 2013.

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