

# Role of prulifloxacin in the treatment of acute rhinosinusitis

## Ruolo di prulifloxacin nel trattamento della rinosinusite acuta

Desiderio Passali<sup>1</sup>, Anna Crisanti<sup>2</sup>, Luisa Maria Bellussi<sup>1</sup>

<sup>1</sup>Clinica ORL, Università degli Studi di Siena, Siena, Italy;

<sup>2</sup>Istituto di Patologia Clinica, Università Tor Vergata, Roma, Italy

### ■ INTRODUCTION

Rhinosinusitis is a very common disease faced more often by general practitioners than specialists; as inflammatory/infective disease, its prevalence varies with climatic changes and seasons, and in presence of other predisposing factors (such as allergy, cigarette smoke exposure, air pollution and gastro-esophageal reflux).

According to a national survey, in the USA upper respiratory tract infection is the third most common cause of a primary care consultation, of which a third is attributable to ARS [1]. In a retrospective population study at three health care centres in Iceland the incidence of ARS is 3.4 cases per 100 inhabitants per year, and 1 in 29.4 patients visit their GP due to ARS. This incidence seems to be similar to other western Countries [2]. According to a multinational questionnaire survey among Asian physicians, 6-10% of patients present at GP, otolaryngologist or paediatric outpatient practices with ARS [3].

In a recent paper, data from two Dutch general practice registration projects (Continuous Morbidity Registration CMR and the Transition Project TP) are reported: in the TP, acute and chronic rhinosinusitis are coded as one diagnosis, whereas in the CMR a separate code for chronic rhinosinusitis exists, but is not in use; as a whole, patients who visit their general practitioner with "symptoms/complaints of sinus", and "other dis-

eases of the respiratory system" have the highest chances to be diagnosed with rhinosinusitis irrespectively from a diagnosis of allergic, viral, bacterial, acute or chronic inflammation [4].

Thus, despite the high prevalence and significant morbidity, the lack of a generally accepted definition for rhinosinusitis and the different diagnostic means (signs/symptoms, endoscopy, CT, bacteriological sampling and testing for allergy) used by GP and other practitioners (allergologists, pulmonologists, pediatricians etc.), are liable of patients with rhinosinusitis often deprived of optimal care.

The European Position Paper on rhinosinusitis and Nasal Polyps, (EPOS) is the first combined guideline for primary and secondary medical care [5].

The EPOS statements for GP are suggested by the diagnosis made on clinical presentation and the need to address to antimicrobial therapy, in absence of microbiological sampling or other instrumental tools, only patients with high suspicion of bacterial episodes.

Nowadays, the wide range of available antibiotics have dramatically reduced the incidence and the related mortality of rhinosinusitis complications; in some cases however, signs and symptoms don't allow a clear differentiation from viral, post viral or bacterial infection or from mild and severe presentation, so that recurrences or even complications, requiring prompt recognition and management can still develop from untreated or inadequately treated sinusitis.

This situation compels GP and family doctors, often weighed down by work, to a careful choice and use first of the best antimicrobial treatment.

Corresponding author

Desiderio Passali

E-mail: d.passali@virgilio.it

Although it remains difficult to determine which patients should receive antibiotics, a meta-analysis evaluating the benefits of antibacterials versus no antibacterials in the treatment of known or suspected bacterial episodes of sinusitis, clearly showed a significant efficacy, on clinical cure and treatment failure outcomes, in favour of this treatment versus placebo [6].

In a more recent Cochrane review, six placebo controlled studies were analysed with clinical failure defined as lack of total cure, as outcome: there was a significant difference in favour of antibiotics compared to placebo at 7 to 15 days follow up [7]. As antibiotics for ARS should be reserved for selected patients with substantial probability of bacterial disease, the choice of the antibiotic effective on causal pathogens (*Streptococcus pneumoniae* and *Haemophilus influenzae*) is of great importance. In agreement with reviews and meta-analysis, guidelines on rhinosinusitis recommend that if a decision is made to treat Acute Bacterial Rhinosinusitis (ABRS) with an antibiotic agent, the clinician should prescribe amoxicillin as first-line therapy for most adults [8, 9].

However, other parameters should be considered in addition to the most narrow-spectrum agent active against the likely pathogens: according to a meta-analysis by Falagas, particularly for patients without severe disease and complicating factors, fewer adverse events, better patient compliance, lower rates of resistance development and fewer costs are also important [10].

The rationale for using antibiotics other than amoxicillin for ABRS can be summarized as follows:

- a) knowledge of pathogens and their resistance profiles;
- b) improved understanding of antibiotics pharmacology, guiding dose and administration route.

These considerations should be supported by double-blind studies evaluating antibiotics versus placebo or comparative studies evaluating beta-lactams versus macrolides; the use of newer drugs, such as fluoroquinolones, should be discussed also in terms of efficacy, safety and costs [11].

The U.S. guidelines on antimicrobial treatment for acute bacterial rhinosinusitis previously published in 2000 were revised in 2004 to consider further resistance changes of respiratory bacteria

(12, 13). In this occasion patients with ABRS were divided in 2 categories:

- a) patients with mild disease who had not received antibacterials in the previous 4-6 weeks;
- b) patients with mild disease treated with antibacterials within the past 4-6 weeks and those with moderate disease regardless of recent antibiotic exposure. Patients of last category are more likely to be infected with a resistant microorganism.

According to this categorization, the respiratory fluoroquinolones were positioned for use in patients with moderate or severe disease, but also in those with mild disease and a history of recent antimicrobial use in an environment of antimicrobial resistance [14].

Fluoroquinolones have an excellent spectrum which covers the most important respiratory pathogens, including atypical and typical pathogens. The pharmacokinetic and dynamic properties of fluoroquinolones have a significant impact on their clinical and bacteriological efficacy. They cause concentration-dependent killing with a sustained post-antibiotic effect [14].

Comparative studies with other antibiotic compounds, show a clinical efficacy and eradication rate for fluoroquinolones in upper airways infections comparable, if not superior, against the commonest respiratory pathogens with lower resistant strains.

In a randomized comparative study, ciprofloxacin or penicillin V were used to treat 80 adult outpatients suffering from otitis media, peritonsillitis or sinusitis: in the ciprofloxacin treated group there were fewer resistant strains; both treatment were well tolerated but ciprofloxacin was superior to penicillin V in eradication rate as well as in clinical efficacy [15].

A randomized double blind study was conducted in a sample of 382 patients with the aim of comparing the efficacy and safety of sparfloxacin with that of cefuroxime axetil in the treatment of acute purulent sinusitis in adults. Efficacy was assessed according to a combination of clinical, bacteriological and radiological variables, both at the end-of-treatment and the follow-up visit after 29 days. The study demonstrated in this well-defined population of outpatients that sparfloxacin could be a suitable empirical antibiotic treatment of acute purulent sinusitis. It may be a particularly appropriate choice in countries where there is a high incidence of  $\beta$ -lactamase-producing strains of *H. in-*

*fluenzae* or *S. pneumoniae* strains that are not fully susceptible to penicillin. Moreover, sparfloxacin can be administered once daily for five days, a shorter regimen than the 7 to 14 day course generally necessary for other antimicrobial agents used to treat this infection improving the patient compliance [16].

Moxifloxacin was tested in a multicenter, prospective, randomized double blind, phase III trial [17]. ABRs was defined by clinical, radiologic and bacteriologic criteria. Only the modified intent-to-treat population (mITT) (118 patients with positive culture for one of five pre-specified pathogens) were evaluated for the primary (clinical response at test-of-cure at the end of therapy) and secondary (improvement in SNOT-16 score) outcomes. Although moxifloxacin 5 day therapy was not statistically superior to placebo for the primary end point, significantly greater improvement was reported by the patients receiving moxifloxacin in SNOT-16 score as well as in concomitant medicine use. Of not secondary importance, no increase in adverse events was observed.

#### *Prulifloxacin*

Among respiratory fluoroquinolones, prulifloxacin, the lipophilic pro-drug of ulifloxacin has been developed to manage urinary and respiratory tract infections.

This antimicrobial agent, thanks to its broad spectrum of antibacterial activity and pharmacokinetic/pharmacodynamic characteristics, is the most up-to-date answer to the questions posed in the treatment of ABRs.

In addition, its immunomodulating effect on cytokine production and release by humans polymorphonuclear neutrophils may tone down the natural predisposition of the inflamed sinuses mucosa to a secondary bacterial infection [18].

In an international multicenter randomized double blind controlled parallel phase III trial, the efficacy of prulifloxacin in the treatment of ABRs versus levofloxacin both orally administered was analyzed. Nineteen European Centres participated at the study for a total of 328 (age range 18-88 years) enrolled patients. Patients were enrolled if affected by moderate/severe rhinosinusitis according to the clinical and instrumental criteria of the EPOS 2012 [5]. After diagnosis, enrolment and randomization, prulifloxacin and levofloxacin were administered at the dosage of 600 mg

or 500 mg once a day for 10 days, respectively. Clinical evaluations were made at 5-7 (V2) and 14-18 days from the therapy start or 4-8 days after the therapy end (V3). Primary endpoint was the test of cure at V3. The therapeutic success was defined as: cure (disappearance of one pre-treatment sign/symptom used for diagnosis and no worsening of others; failure (lack of at least one sign/symptom resolution or worsening of others; undetermined (when circumstances didn't allow the clinical response evaluation). At 25-35 days follow-up the efficacy on time free from recurrences, QoL and safety profiles were also determined. As regards distribution, no significant difference in signs and symptoms was found at baseline between groups. On ITT population, the clinical efficacy 4-8 days after the treatment end was 89.9% in the prulifloxacin group versus 90.9% in levofloxacin group with no statistically significant difference. Similarly, no statistically significant differences were observed in persistent recovery (or time free from recurrences) and QoL. In both treatment groups adverse events were scanty, with only one severe adverse event in the levofloxacin treated group.

Global clinical evaluation was very good in 71.3% of patients treated with prulifloxacin and 69.9% of levofloxacin treated patients [19].

From this trial, the favourable pharmacokinetic profile of oral prulifloxacin can be inferred: after oral administration of a single dose of 600 mg prulifloxacin, ulifloxacin, the active metabolite reaches the maximum plasma concentration ( $C_{max}$ ) 1.6  $\mu\text{g}/\text{mL}$  after 1 hour exceeding the 90% minimum inhibitory concentration ( $MIC_{90}$ ) values of common respiratory pathogens. The  $T_{1/2}$  10.7 h allows the once a day administration with an increased compliance of the patient.

After absorption from the gastrointestinal tract, prulifloxacin is rapidly and extensively metabolized to form ulifloxacin, which is predominantly eliminated unchanged by renal excretion. 48 hours after a single oral 600 mg dose of prulifloxacin the urine concentration of ulifloxacin still exceeds the  $MIC_{90}$  of urinary pathogens. Although the plasma levels of ulifloxacin are not higher than 2  $\mu\text{g}/\text{mL}$ , the concentrations detected in some tissues and fluids are greater and long lasting than those found in the circulating blood. Concerning the respiratory tract infections, a research study was performed to evaluate the distribution in

lung tissue of ulifloxacin after oral administration of prulifloxacin in a single 600 mg dose: drug tissue concentrations represent a valid aid in the interpretation of clinical efficacy data not fully explainable on the basis of MICs and plasma levels alone. In this study lung tissue concentrations consistently exceeded those in plasma throughout the 24 hour sampling period supporting the efficacy data reported in clinical trials performed in patients with exacerbation of chronic bronchitis treated with prulifloxacin [20]. Same results were obtained when evaluating the concentration of ulifloxacin in sinuses mucosa and plasma of patients with chronic rhinosinusitis requiring elective endoscopic sinus surgery: prulifloxacin, when administered orally in a single 600 mg dose distributes very well in sinuses mucosa where it reaches concentrations significantly higher than in plasma and these findings strongly call for confirmatory clinical trials in patients with bacterial rhinosinusitis [21].

Overall, fluoroquinolones can be considered safe as can be inferred from comparative studies which have evaluated their use in elderly and younger populations. However, because of physiological changes in renal function with age and when certain co-morbidities are present, some special considerations are necessary when using these antimicrobial agents.

The most frequent adverse event of their use are reactions of the gastrointestinal tract such as nausea, dyspepsia, vomiting or diarrhoea, but diarrhoea is less frequent than treatment with other classes of antimicrobials.

A rare effect is QT-prolongation which may result in serious arrhythmias. Moxifloxacin has a several fold higher risk of cardiac arrhythmias than levofloxacin or ciprofloxacin whereas according to the European Medicines Agency (EMA) the lower risk is shown by prulifloxacin. However, it is important for the prescriber, not only to know the relative risks, but also to focus on the incidence of serious arrhythmias. Trials providing data on the relative risk and on the incidence of adverse cardiac events among commonly used fluoroquinolones show inconsistencies and rarity of events. Thus, the choice of the best antimicrobial agent should be based on the concern for a cardiac arrhythmias only in patients at the highest risk of such an event, carefully weighing efficacy and adverse events [22].

Penetration of ulifloxacin into the CNS is poor, with low or no concentrations of ulifloxacin detected in cerebrospinal fluid after single or multiple dose administration of prulifloxacin. This antimicrobial agent is thus free from the excitatory effects of other quinolones and the neurologic adverse reactions of particular concern in patients with impairment of CNS such as severe cerebral arteriosclerosis or epilepsy [23].

Among the fluoroquinolones family, prulifloxacin shows a safety profile which makes it the best treatment option in elderly patients.

This favourable safety profile makes its administration easier, with no special considerations in different patients categories: elderly patients with physiological changes of renal function don't need specific restriction of dosage or posologic changes.

In women, recently the importance of intact vaginal communities in resistance to urogenital infection has been highlighted. Many factors may modify the vaginal microflora and among these a significant association has been reported between antibiotic therapy and vulvovaginitis: treatment with amoxicillin-clavulanic acid increases vaginal pH and reduces the lactobacillary component of vaginal microbiota so important for vaginal microbiota balance [24].

On the contrary, the repeated administration of prulifloxacin 600 mg tablets doesn't affect neither the pH nor the lactobacillary component of the vaginal microbiota in healthy fertile women [25].

In patients with co-morbidities in multiple treatment, the once daily administration of prulifloxacin which supports a better patient compliance and adherence, should be considered a key factor for a successful antibiotic treatment.

The simple posologic schedule as single dosage (600 mg) once a day, the clinical efficacy, as well as the bacteriological eradication and the safety of prulifloxacin are supported by several *in vitro* and *in vivo* studies and these characteristics are key factors for a successful antibiotic treatment in ABRS.

Clinical cure, bacteriological efficacy, safety, easy and simple administration are four characteristics making prulifloxacin a reliable and resolving antibiotic in the treatment of ABRS.

*Keywords:* prulifloxacin, acute rhinosinusitis.

## SUMMARY

Acute rhinosinusitis (ARS) is a very common disease faced more often by general practitioners than ear, nose and throat specialists, pneumologists or allergologists. In an outpatients' setting, upper respiratory tract infection is the third most common cause of a primary care consultation, one third of which is attributable to ARS, diagnosed upon clinical presentation. In some cases however, signs and symptoms do not allow clear differentiation from viral, post-viral or bacterial infection. This compels GPs and family doctors to make a careful choice and first use the best antimicrobial treatment to avoid recurrences or complications and the rise of antibiotic resistance. Amoxicillin, thanks to its narrow spectrum against likely respiratory pathogens, is recommended as first-line therapy to treat acute bacterial rhinosinusitis by several international guidelines, being safe at the same time. Other antibiotics (beta-lactams, macrolides and newer drugs, such as fluoroquinolones) have been evaluated in double-blind studies versus placebo or comparative studies in terms of efficacy, safety and costs. Prulifloxacin, the active metabolite of ulifloxacin, is an oral fluoroquinolone with a

broad *in vitro* activity spectrum against Gram-positive and negative bacteria and among fluoroquinolones has the lowest power of inducing resistance. *In vitro* and *in vivo* studies have shown its clinical efficacy and pathogen eradication. Ulifloxacin  $T_{1/2}$  and plasma and tissue concentrations including the nose-paranasal sinuses mucosa allow once daily administration at the dosage of 600 mg.

Prulifloxacin shows a high safety profile: it is the fluoroquinolone with the lowest risk of cardiac arrhythmias for prolongation of the QT interval; the CNS penetration is negligible; in women prulifloxacin does not affect the lactobacillary component of the vaginal microbiota, lowering the risk of genito-urinary tract infections. The pharmacokinetic characteristics and safety profile of prulifloxacin make it the antibiotic option with the best potential to achieve clinical cure and bacteriological eradication, well tolerated and safe without specific restriction or posologic changes in the elderly and in patients with co-morbidities in multiple treatment, hence resolving ARS reliably and being simple and easy to administer.

## RIASSUNTO

La rinosinusite acuta è patologia frequente, diagnosticata e trattata più spesso dal medico di medicina generale che dagli specialisti otorinolaringoiatri, pneumologi o allergologi.

In un setting ambulatoriale nel quale le infezioni delle vie aeree superiori rappresentano la terza causa di consultazione in ordine di frequenza, un terzo delle visite è attribuibile a rinosinusite acuta.

La diagnosi di rinosinusite è prevalentemente clinica e gravata da difficoltà di diagnosi differenziale tra forme virali, infiammatorie post-virali ovvero chiaramente batteriche.

In tale ambito, la prescrizione di una corretta terapia antibiotica risulta fondamentale per evitare trattamenti inappropriati con possibilità di insorgenza di resistenze batteriche, ma nello stesso tempo per evitare ricorrenze o complicanze talora anche gravi.

Diverse linee guida internazionali raccomandano quale terapia di prima linea per il trattamento della sinusite acuta batterica l'amoxicillina per il suo selettivo spettro d'azione nei confronti dei comuni patogeni respiratori e perché scevra da importanti effetti collaterali. Altre molecole antibiotiche ( $\beta$ -lattamici, macrolidi e i più nuovi fluorochinoloni) sono stati testati in trial in doppio cieco verso placebo o comparativi per valutarne efficacia, effetti collaterali e costi.

Prulifloxacin, profarmaco di ulifloxacin, è un fluorochinolone orale con un largo spettro di attività *in vitro* nei con-

fronti di numerosi microrganismi Gram-positivi e Gram-negativi e, fra i fluorochinoloni, ha il potenziale più basso di indurre l'emergenza di ceppi resistenti.

L'emivita e il picco delle concentrazioni ematiche e tessutali, inclusa la mucosa naso-sinusale, ne giustificano la monosomministrazione al dosaggio di 600 mg.

Studi *in vitro* e trial clinici ne hanno dimostrato l'efficacia sia clinica che batteriologica.

In uno studio multicentrico di fase III randomizzato controllato in doppio cieco a gruppi paralleli il trattamento con prulifloxacin 600 mg/die ha mostrato una efficacia clinica e un profilo di sicurezza sovrapponibili a quelli di levofloxacin.

Prulifloxacin è il fluorochinolone che meno di tutti gli altri espone al rischio di aritmie cardiache per allungamento dell'intervallo QT; l'assorbimento a livello del SNC è trascurabile; nelle donne, prulifloxacin non interferisce con la componente lattobacillare vaginale, riducendo il rischio di infezioni del tratto genito-urinario.

Per le caratteristiche di farmacocinetica e per il profilo di sicurezza, prulifloxacin deve pertanto considerarsi antibiotico clinicamente efficace e in grado di eradicare i comuni batteri patogeni, ben tollerato, sicuro poiché non sono richieste particolari attenzioni o modifiche di dosaggio nei pazienti anziani e nei poli-trattati, quindi risolutivo, affidabile e di facile e semplice somministrazione.

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