Peer reviewed article

Macrolide antibiotic therapy in patients with cystic fibrosis

Martin H. Schöni

Summary

This summary of the current knowledge of macrolide therapy serves as an example of recent progress in the therapeutic approach to treating patients with cystic fibrosis (CF). The benefit of macrolides in the treatment of patients with diffuse panbronchiolitis and *Pseudomonas aeruginosa* infections, as seen in Japan, was the rational behind trials in patients with CF. Thus far, the majority of reports of positive trends in the therapeutic potential of macrolides have studied azithromycin. The data presented in peer reviewed journals are, however, too sparse to already justify firm recommendations for the general use of azithromycin, erythromycin or clarithromycin on a long-term basis for the treatment of chronic lung disease in CF.

Key words: cystic fibrosis; macrolides; azithromycin; Pseudomonas aeruginosa; chronic lung disease; diffuse panbronchiolitis

Introduction

Cystic fibrosis (CF) continues to be an attractive disease for research both in basic science and in clinical application. A search of the PubMed database (National Library of Medicine, USA) for unlimited citations using the key word "CF" found a total of 20'262 publications. At the end of March 2003 using limited search items "macrolides and cystic fibrosis" 80 articles and for the more specific key word "azithromycin and cystic fibrosis" 17 published papers were listed.

Current knowledge of the pathophysiology of cystic fibrosis indicates that intracellular generation, processing, degradation and function of the chlorid channel protein (called cystic fibrosis transmembrane regulator: CFTR) is responsible for the defective electrolyte composition found in reabsorbing and secreting epithelia. More than 1000 genetic mutations have now been detected influencing at least five different classes of intracellular defects for the CFTR protein [1]. In spite of there being several hypotheses for the pathophysiology of airways disease associated with CF, a unique accepted explanation for the pulmonary phenotype has not yet emerged. It seems that altered airways surface liquid, arising as a consequence of CFTR dysfunction, may predispose to bacterial adherence and consequently results in an augmented inflammatory response. Current research activities are mainly focussed on understanding this inflammatory process, which, having started seems to determine the fatal outcome. Whether this inflammation in the lung very early in childhood is a primary event due to the basic genetic defect or is a consequence of early infectious triggers is still debated [2, 3]. However, there is a significant body of evidence that the level of inflammation directly correlates with progression and outcome of the illness [4]. Furthermore, the function of inflammatory cells may also be dysregulated in patients with CF. The sum of these effects, in addition to the impairment of mucociliary clearance and of innate immune defences, all contribute to the development of lung destruction, lung cystic lesions, bronchiectasis and chronic *P. aeruginosa* colonisation and infection.

During the last 10 years the therapeutic approach to chronic lung disease has little changed on the basis of principles. The mainstay in pulmonary therapy bases on physiotherapy, ie, bronchial clearing, inhalations, ie, application of a variety of medications (bronchodilators, antibiotics, DNase, steroids), and enteral or parenteral antibiotics to fight against bronchial infections. The special indications and the handling of the latter has recently been published in an extensive consensus report of the European CF Society [5]. One new aspect will be addressed in detail here: the use of azithromycin for infection control and inflammation modulation.

No financial support declared.

Macrolide therapy for diffuse panbronchiolitis and CF

In 1987 Kudoh et al. reported in a Japanese journal that low dose long-term erythromycin therapy could reduce the progression of diffuse panbronchiolitis (DPB) [6]. Diffuse panbronchiolitis is a chronic inflammatory pulmonary disease seen mainly in Japan. It was first characterised by Yamanaka in 1969 and described in detail by his colleagues in 1983, in the journal Chest [7]. Patients with this disease suffer from chronic cough with mucopurulent sputum, wheezing and exertional dyspnoea. Typically in the chest x-ray disseminated reticulonodular densities are prominent with hyperinflation, whilst in computed tomography small rounded areas of attenuation with centrilobular distribution and hypoattenuation in the periphery are typical. The lung function is characterised by chronic airflow limitation with prominent bronchodilator resistance. The disease resembles CF in as much as sputum is positive for *H. influenzae* in the beginning and subsequently *P. aeruginosa* can be cultured. Patients also have signs of systemic inflammation with raised erythrocyte sedimentation rate, elevated C reactive protein (CRP) and in 40% rheumatoid factor is positive. If DPB is not treated it leads to death with a 10 year survival of only 12.4–21.9% for those patients who are infected with *P. aeruginosa*. Interestingly this *P. aeruginosa* is of the mucoid type, as observed in patients with CF. There are a lot of similarities between CF and DPB not only the clinical and phenotypic presentation but also several research results. In both diseases the chronic colonisation with *P. aeruginosa* is one of the unexplained characteristics of the chronic destructive lung disease. The production of a biofilm by alginate synthesis of mucoid *P. aeruginosa* seems to be a defense and survival strategy of these bacteria against antibiotics in both diseases. Biofilms are matrix-encased communities of bacteria which are specialised for surface persistence. In these biofilms bacteria can resist antibiotics and host defence mechanisms [8, 9]. In CF as well as in DPB neutrophils and IL-8 cytokine concentration are elevated in bronchoalveolar lavage (BAL) fluid, an increased level of defensins are seen in BAL fluid in DPB whereas it is decreased in CF patients [10–12]. The most common CF mutation ΔF508 has not been identified in DPB, however DPB was closely associated with some rare mutations of the CFTR gene [13, 14]. As in CF patients chronic sinusitis is almost always found in patients with DPB, too.

The DPB trials

After case descriptions and following open as well as randomised clinical trials the beneficial effect of low dose, long term (at least 6 months) treatment with 400 mg to 600 mg erythromycin daily was documented in patients with DPB and *P. aeruginosa* infection. The clinical effect was impressive, resulting in an increase of 10 year survival from 12.4% to more than 90% [15, 16].

The reason behind this dramatic effect was subject of intensive research. In summary the anti-inflammatory mechanism of macrolides seems to be based on: a) modulation of inflammatory pathways by decreasing neutrophils and IL-8 in bronchial secretions, by decreasing the superoxide generation in the lung tissue and diminishing tumour necrosis factor alpha (TNF-α) production as well as by attenuating leucocyte migration, b) antibacterial effects through inhibition of alginate and biofilm formation, inhibition of adherence of *P. aeruginosa* to the bronchial wall by influencing flagella synthesis and motility and finally c) up-regulation of the chloride transport by the CFTR [17]. These effects were seen after treatment with erythromycin, roxithromycin, clarithromycin and azithromycin and the improvement in the clinical state of the patients started after 2 months of the beginning of a low dose therapy.

The CF trials

The similarities in DPB and CF prompted some single case treatments in patients with CF in 1997. Everard and co-workers reported their one month pilot study with 200 mg t.d.s. erythromycin in CF patients and showed, that IL-8 levels and neutrophil elastase in sputum decreased significantly. However, clinical data of the 6 patients were not provided [18].

From 1997 to 2003 ten studies including 339 patients with CF who were treated with macrolides (8 studies with azithromycin, one with erythromycin, one with clarithromycin) were either published as abstracts (4 studies) or as peer reviewed manuscripts (5 studies). One multicentre trial so far was made available as a press release and as "Congress Highlights" CD of the North American Cystic Fibrosis Foundation on their internet homepage (www.cff.org) (table 1) [19–26].

The duration of treatment was one to 33 months, predominantly 3–8 months, and the outcome variables differed as follows: in 8 studies lung function was the major endpoint, in one study IL-8 in sputum, and in an other the influence of azitromycin on the buccal adherence of *P. aeruginosa*. The dosing regimens were different, azithromycin was mostly applied in a dose of 250 mg either two or three times a week, but in some trials daily dosage was applied. In the largest multicentre trial including 23 CF Foundation-accredited care centres in the USA, 251 CF patients were initially screened for their eligibility to be included in the study. 185 were allocated, 98 received placebo, 87 azithromycin, in a dose of 250 mg three times a week for those with a body weight below 40 kg and 500 mg three times a week with a body weight above 40 kg.

FEV_1 and/or FVC rose in all studies between 4.8% to 11% of predicted values from baseline, however only 3 studies were fully placebo con-

Table 1

Published studies about macrolides and cystic fibrosis including press released and reported data of the US trial [26]. References of the studies see text.

n	duration	drug/dose	outcome	reference (ref.)
6	1 m	Eryt. 200 mg t.d.s.	IL-8 decrease	Everard ML, ERJ 10:2926, 1997, Perth, Australia [18]
7	0.3–1.2 yr	AZM, daily, dose n.g.	FEV_1 11.0% and FVC 11.3% increase	Jaffe A, Lancet 352:420, 1998, London, UK [19]
14	16–33 m	AZM, 250 mg 3× week	FEV 5.8% and FVC 4.8% increase	Anstead MI, Pediatr Pulmonol 19: 1999, Abstract Lexiton USA [22]
18	3 m	AZM, 250 mg 3×/week	FEV_1 2.2% and FEV 5.7% increase	Pirzada OM, Pediatr Pulmonol 19: 1999, Abstract Sheffield UK [23]
7	6 w	Clarithromycin 500 mg b.i.d.	FEV 18 ± 11% and FVC 7 ± 10% increase	Ordonez CL, AJCCM 159:680, 1999 Abstract and Ped. Pulmonol 32: 29–37, 2001 San Francisco, USA [21]
11	3 m	AZM 250 mg 2×/week	*P. aeruginosa* adherence to buccal cells reduced	Baumann U, Infection 29:7, 2001 Hannover Germany [20]
41	6 m	AZM, 250 mg/d or 500 mg/d or placebo	Difference of FEV_1 AZM vs. placebo: 5.4% (CI 0.8–10.5%)	Equi A, Lancet 360:978, 2002, London UK [25]
60	3 m	AZM, 250 mg/d or placebo	Reduced rate of decline of FEV_1; plazebo –5.73%, AZM –3.62%	Wolter J, Thorax 57:212, 2002 Brisbane, Australia [24]
50	8 m	AZM, 250 mg/d	Mean change in FEV_1 + 1.07% compared to 12 months before treatment –1.06%	Hansen CR, Pediatr Pulmonol 24:2002, Abstract, p. 287, Copenhagen, Denmark [27]
185	6 m	AZM 250 mg or 500 mg 3×/week or placebo	FEV_1 increase 6.21%, 40–50% reduction of hospital days	Marshall et al. Press release and Highlight CD of CF Foundation, Washington, USA

trolled randomised trials [24–26]. The US study reported an overall treatment effect of 6.21% (intention to treat) on FEV_1 improvement at the end of the 6 months period [26]. On the active treatment arm the average change of FEV_1 to baseline measured at the beginning of the treatment was 4.44% compared to –1.77% on the placebo arm. This difference was statistically significant.

The treatment was well tolerated and side effects were not recorded. In general it was reported that the presence and density of *P. aeruginosa* did not change. However, according to the abstract published in Pediatric Pulmonolgy of Hansen et al. the percentage of sputum samples containing mucoid colonies was 73.9% before treatment, decreasing to 67.1% during treatment ($p < 0.002$) [26]. Changes in bacterial densities and in the appearance of other micro-organisms, other than those usually cultured from CF bronchial secretions (ie, *Haemophilus influenza and Staphyloccocus aureus*), were not reported.

In all the published reports the general conclusion was, that more and longer lasting randomised, placebo controlled studies should be carried out to evaluate the sustained effect of this therapy. The results of the study announced by A. Clément, a phase III trial in 260 cystic fibrosis patients in Paris, are not yet available.

In 2002 the Australian group from Brisbane published their randomised placebo controlled trial with 30 adult CF patients [24]. They used 250 mg azithromycin every day for 3 months and evaluated lung function, body mass index as a marker for nutrition, quality of life with a standardised questionnaire, inflammation markers in blood (sedimentation rate and CRP) and analysed sputum for bacteria. 21 patients in the placebo and 24 in the medication group, mean age 27.9 ± 6.5 years, completed the study. Patients had a mean (± SD) FEV_1 of 62.3 ± 24.8% and a FVC of 77.5 ± 19.9 in the placebo group and the corresponding values in the azithromycin group were FEV_1 50.9 ± 18.3% and 67.3 ± 19.0%, respectively. Mean (± SD) changes in FEV_1 (in % predicted over time – azithromycin group [placebo group]) were 2.3 (± 7.7) [–1.32 (± 5.5)] for the first month, 1.5 (± 8.8) [–1.17 (± 5.8)] in the second month and 2.9 (± 9.2) [–0.91 (± 5.9)] in the third month. There was a mean (± SE) FEV_1 excess effect of azithromycin over placebo of 3.62 (± 1.78)% (95% confidence interval –7.13 to –0.13%) and a mean (± SE) FEV excess effect of 5.73 (± 1.6)% (95% confidence interval –8.98 to –2.47%) (p-value drug versus placebo for $FEV_1 = 0.047$ and for FVC = 0.001). A statistically significant outcome between the two groups was also reported for number of courses of intravenous antibiotics, total iv. antibiotic dose, total days of home iv. and total days in hospital. Sedimentation rate and CRP in blood decreased, quality of life scores increased and the microbiology of bronchial secretions remained unchanged in the azithromycin group. Despite the limitations for the trial due to the heterogenous and small patient groups, despite the large range of lung function measurement results in both groups at the entry to the study and despite the rather short observation period, improvements appear to have occurred in those who were treated with azithromycin. The conclusions drawn by the authors were speculative suggesting that long-term azithromycin treatment might have a significant beneficial impact on morbidity and mortality.

In their randomised, placebo-controlled crossover trial, Equi A. et al., from London conclude, that a 4 to 6 month trial of azithromycin is justified in children who do not respond to con-

ventional treatment [25]. Forty one children between 8 and 18 years of age participated in the 15-month placebo controlled study and received either 250 mg daily (body weight <40 kg) or 500 mg daily. The primary outcome variable was the median relative difference in FEV_1 between the azithromycin and placebo treatment periods which was 5.4% (95% CI 0.8–10.5%). 17 of 41 patients had 24 fewer oral antibiotic courses during azithromycin treatment than when taking placebo ($p = 0.005$). All other variables which were assessed (sputum bacterial densities, inflammatory markers, exercise tolerance and subjective well-being measured by a CF-validated quality-of-life questionnaire) did not change during the active treatment period. Compared to the study from Brisbane in which the mean age of patients was 27.9 years (range 18–44) median age in the study by Equi A et al. from London was 13.8 years (range 8.1–18.6). The different outcome in the quality-of-life reports (improvement in the Wolter J. study) seems to be predominantly due to age.

In the American multicentre study of the CF Foundation the mean age of the patients was 20.2 years and the patients had a mean FEV^1 between 68.3% and 70.6% predicted (treatment and placebo group, respectively) [25]. All patients had *P. aeruginosa* in a mean density of 7.4 log10 CFU and 89% in the azithromycin group and 92% in the placebo group were of the mucoid type. *Staph. aureus* in the sputum was seen in 49% (placebo) and 60% (treatment) of the patients, respectively. The mean absolute change of FEV_1 in litres after 168 days of treatment was 0.097 litres in the azithromycin group and 0.003 litres with placebo, resulting in a treatment effect of 0.093 litres ($p = 0.009$); expressed as % predicted, this treatment effect was 6.21%. This improvement was already seen at day 28 of therapy and was sustained. There was also a 40% reduction of exacerbations from pulmonary symptoms, the number of iv. antibiotic courses was lowered by 40% resulting in a 52% reduction in hospitalisations and a 32% reduction of oral quinolone use. However, the quality-of-life factors did not change significantly. There was no eradication of pathogens in the sputum in the treatment group but a reduction in the density of *P. aeruginosa* of 0.5 log10 CFU was observed. In the azithromycin group nausea (33%), diarrhoea (20%) and wheezing (17%) was significantly more frequently reported than in the placebo group. All laboratory variables (ie, haematology, liver and kidney function) remained normal, there was no increase of hearing loss or tinnitus or an increased rate of rashes or arthraglia. There was good adherence to the treatment, in both groups a dose reduction in 4 patients was necessary due to moderate side effects.

The rationale behind using azithromycin in CF patients was first guided by the observations from the successful treatment of DPB. As stated at the North American CF Congress in New Orleans in November 2002 azithromycin was also chosen because the drug is well absorbed and not affected by food intake, important in patients with pancreatic insufficiency. The drug is not metabolised by the cytochrome P450 system, has a long half-life and a marked accumulation in lungs and sputum and exerts a major activity against many respiratory pathogens. It is also already licensed and easily available, has an acceptable safety profile in children and adults and is tested in long-term use in patients with non-tuberculous mycobacterial disease [26].

The effect of macrolides in patients with CF is not clear [28, 29]. Since there is no documented in vivo and in vitro bacteriostatic or bactericidal action on *P. aeruginosa* by macrolides the current knowledge indicates that an anti-inflammatory effect is probably responsible for the clinical improvements in patients with CF and chronic *P. aeruginosa* infection [28–30]. Recent evidence for efficacy also comes from observations that macrolides inhibit endotoxin A, total proteases, elastase, phospholipase C, DNase, lecithinase, gelatinase, lipase, pyocyanin and motility of *P. aeruginosa*. Proteases and elastase in the lung are thought to be mainly responsible for chronic lung destruction in CF patients. A decrease of the elastase burden to the lung lessens the destructive process. Assuming the process can be slowed down by macrolides, the therapeutic approach could be substantially simplified. The influence of macrolides on biofilm formation and the observation that combining macrolides and ciprofloxacin was far more effective at reducing *P. aeruginosa* in vitro, creates new possibilities for oral treatment of chronic *P. aeruginosa* infection in CF patients.

The results of the US trial were comparable to the two randomised placebo controlled studies from London and Brisbane. Therefore, the suggestions made from the US trial for macrolide therapy were cautiously formulated, too. Therapy was recommended as an option in patients older than 6 years of age with chronic infection with *P. aeruginosa* as an adjunct to the other proven CF therapies such as inhalation of tobramycin and anti-inflammatory therapy with ibuprofen. In the US trial 63% of the patients also received inhaled tobramycin together with azithromycin and 16% to 26% (placebo group) were on oral ibuprofen. It was recommended that pulmonary function be assessed, and the number of exacerbations and weight after 24 weeks of treatment should determine the need for continued azithromycin. There was no suggestion for a general switch of patients on to this treatment.

Randomised controlled trials (RCT) in CF

In recent years the need for starting long term controlled randomised trials (RCT) according to Cochrane's criteria for clinical research questions in CF was recognised. From the Cochrane CF Study group it became evident, that in most fields of CF, trials with good power are lacking. Many studies are conducted over an insufficient period

of time. In most instances no outcome measures are defined and the time for publication of significant data is too long. K. Cheng and co-workers hand-searched 199 abstracts about CF from 44 journals published between 1969 and 1995 [31]. 178 manuscripts were eventually analysed, but none of these abstracts on clinical trials fulfilled the modern criteria for a RCT trial. Of these abstracts only 32% resulted in a publication in a peer reviewed journal and of these 32% only 8% were published within one year, 29% within 2 years, and 40% within 5 years of the appearance of the abstract. When the abstracts were stratified according to sample size, or positive or negative outcome, no change in the above results were observed. There is also no single study published so far in which there is scope for applying "evidence based medicine". Of 506 trials which were labelled RCT, 72% had a sample size with less than 30 patients and only 8.7% were multicentre studies [32].

Despite a significant increase in published material about new CF therapies, the direct clinical benefit from these research results is still rather poor.

It is hoped, that more clinical trials are subsequently carried out using the RCT design, so as to speed up the time taken for bringing new drugs from bench to bedside.

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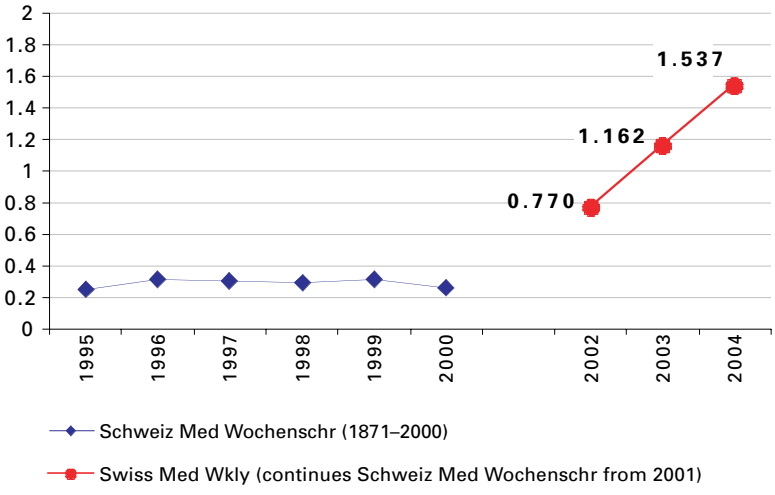

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