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Bronchiectasis in children in association with mycophenolate mofetil

Introduction

Cellcept[®], with mycophenolate mofetil (MMF) as active substance, was granted a marketing authorisation on 14 February 1996. On 16 July 2001, paediatric transplantations were included in the therapeutic indication. The current therapeutic indication is: *Cellcept is indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.*

The adult dose recommendation of 1 g bid was based on a dose finding study, in which 1.5 g bid revealed more undesirable effects with similar efficacy as compared with the dose of 1 g bid. The paediatric dose recommendation sounds: *Children and adolescents (aged 2 to 18 years): the recommended dose of MMF is 600 mg/m² administered orally twice daily (up to a maximum of 2 g daily). Cellcept capsules should only be prescribed to patients with a body surface area of at least 1.25 m². Patients with a body surface area of 1.25 to 1.5 m² may be prescribed Cellcept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area greater than 1.5 m² may be prescribed Cellcept capsules at a dose of 1 g twice daily (2 g daily dose).*

These recommendations were based on adult pharmacokinetic parameters, presuming that the metabolism and mechanism of action of MMF in paediatric patients would be similar to adults. To decrease inter-patient variability, the paediatric dose recommendation is expressed in mg/m² instead of mg/kg. In contrast with adult patients, paediatric pharmacokinetic parameters could hardly be related to efficacy and safety.

The SPC recommends, outside the immediate post-transplant period, to limit the dosage to 1.0 g bid in case of severe renal impairment (GFR < 25 ml*min⁻¹*1.73 m⁻²) [1].

Reports

One paediatric transplantation centre has reported five cases of bronchiectasis during longstanding use of MMF. One patient was transplanted in another centre and followed-up in the reporting centre. The reporting centre includes about 35 transplanted children. The discovery of one child with bronchiectasis urged the physicians to perform investigations in the other patients with complaints like persistent coughing or repeated respiratory infections.

High resolution CT-scans of the thorax revealed bronchiectasis in patients A, B, D and E, while patient C had bronchiectal dilation. Flow-volume curves revealed diminished maximal end-expiratory flows, consistent with increased damage and/or obstruction of peripheral airways.

None of the patients had any rejection in their last transplant, indicating sufficient immune suppression.

In patient E, recently a mycobacterium tuberculosis was diagnosed several months after the diagnosis of bronchiectasis. A previous bronchoalveolar lavage revealed no tuberculosis.

All MMF dosages are below the recommended dosage of 600 mg/m² bid. However, only patient E fulfilled the requirement of a body surface area above 1.25 m². The percentiles length for age are low, indicating a short stature for age.

Table 1. reports of bronchiectasis associated with the use of MMF

Patient, Sex, age OKD	Type of transplantation duration of MMF therapy	MMF dose [mg] BSA [m ²] dose [mg/m ² bid] percentile length for age [range]	Concomitant immunosuppressive medication	Antibiotics since transplantation
A F, 11 ?	liver 4.0 years	500+500 1.06 – 1.26 470 30	CsA replaced by MMF	maintenance TMP-SMX, later amoxicillin
B M, 13 unknown	renal 3.3 years	500+750 0.95 - 1.15 ± 560 0.6 - 5	steroids, CsA	maintenance TMP-SMX 1 course
C M,7 congenital nephrotic syndrome	renal 3.8 years	400+400 0.70 - 0.83 570 - 480 0.5 - <0.5	steroids, 6 months CsA,	maintenance TMP-SMX 5 courses
D M, 11 nephrotic syndrome	renal 4.5 years	500+500 0.86 - 1.12 578 - 445 15 - 40	steroids, 6 months CsA,	maintenance TMP-SMX 4 courses
E M, 17 obstructive uropathy	renal 3.8 years	500+500 1.36 - 1.49 369 - 336 5 - <0.5	steroids, CsA	maintenance TMP-SMX, maintenance tobramycin inhalations and alternating ciprofloxacin, pheneticillin course, ciprofloxacin course

OKD: original kidney disease, CsA: cyclosporin A, TMP-SMX: trimethoprim -sulfamethoxazole

Other sources of information

Literature

In 1998, Elli et al.[2] reported 5 female renal transplant patients, out of a population of 26 male and 19 female renal transplant patients, with persistent cough, starting 36 - 84 days after initiation of MMF. Chest X-rays were normal, 2 bronchoalveolar lavages revealed no infectious causes, spirometry showed ventilatory obstruction that was irreversible in 2 patients. In one patient a CT-chest was performed, showing bronchiectasis. In all patients, symptoms improved only after MMF was stopped and completely reversed 3 to 4 weeks after discontinuation [2].

Fijo et al. [3] emphasise that the optimal paediatric dose has not been established. He describes 4 out of 36 paediatric patient with persistent, irritative cough. Their immunosuppressive therapy included 0.15-0.20 mg/kg tacrolimus, 26 mg/kg (similar to 765 mg/m²) MMF and steroids. Chest X-rays, bacterial and virological investigations revealed no cause. Tacrolimus plasma levels varied between 7 and 10 ng/ml and mycophenolate acid (MPA, the active metabolite) plasma levels varied between 7 and 14.5 microgram/ml. Coughing disappeared after MMF dose reduction, resulting in MPA plasma levels between 2 and 5 microgram/ml [3].

Recently, Barker reviewed bronchiectasis. He mentions immunodeficiency secondary to immune modulation after transplantation as a condition associated with bronchiectasis [4].

Databases

No other associations between bronchiectasis and drugs have been reported to Lareb. The WHO combination database contained at the end of the first quartile 2002 two drugs in association with bronchiectasis with more than two reports: leflunomide and zafirlukast.

Mechanism

These reports and the literature highlight several aspects of MMF immune suppression in paediatric patients.

Conclusion and considerations

Dose limitation

The dose recommendation for children and adolescents aged 2-18 years is not consistent with the requirement of a body surface area of at least 1.25 m². Assuming growth according to the 50 percentile, such body surface area will be reached at age 12 (Table 2). Children with renal insufficiency have a much lower length for age percentile, as demonstrated in the presented cases (Table 1).

Table 2: linkage between 50th percentile length, weight and body surface area derived from Dutch Growth Study 1997, TNO/LUMC, Bohn Stafleu Van Loghum, 1998. BSA is calculated according to Mosteller [5].

age (years)	7	8	9	10	11	12
P ₅₀ length for age (cm)	126.5	133	138.5	143.5	148	154
P ₅₀ weight for length (kg)	25	28	30	34	36	42
P ₅₀ BSA (m ²)	0.94	1.02	1.07	1.14	1.22	1.34

Dose recommendation

Most patients received MMF in a dose below the dose recommendation of 600 mg/m² bid, combined with steroids and cyclosporin as recommended in the SPC. This dose recommendation is based on assumed pharmacokinetic similarity between adults and paediatric patients. In contrast with adult patients, paediatric pharmacokinetic parameters could hardly be related to efficacy and safety [1]. The presented cases challenge the justification of the paediatric dose recommendation.

Duration of MMF therapy

All patients received longstanding MMF therapy. The EPAR states that the paediatric clinical safety assessment is based on a population of 140 renal transplant paediatric patients. Approximately 78% have received MMF for at least 12 months and approximately 11% for 3 years [1]. The presented cases may indicate that the safety of long-term treatment with MMF differs from the safety of 12-months treatment.

The longstanding immunosuppressive therapy with MMF may have contributed to recurrent pulmonary infections and longstanding coughing, ultimately resulting in bronchiectasis. Altogether, the presented cases with recurrent pulmonary infections, ultimately resulting in bronchiectasis, suggest too strong immune suppression due to the dose recommendation, the duration of MMF therapy, or both. This is supported by the recent mycobacterium tuberculosis infection in one case.

References

1. EPAR Cellcept. <http://www.eudra.org/humandocs/humans/epar/cellcept/cellcept.htm> (Revision 5 14-2-2002, accessed 17 September 2002).
2. Elli A, Aroldi A, Montagnino G, Tarantino A. Mycophenolate mofetil and cough. *Transplantation* 1998;66:409.
3. Fijo J, Martín Govantes J. Micofenolato mofetil y tos en pacientes pediátricos. *Nefrología*. 2000 May-Jun;20(3):297-8.
4. Barker AF. Bronchiectasis. *New Engl J Med* 2002;346:1383-93.
5. Mosteller RD. Simplified Calculation of Body Surface Area. *N Engl J Med* 1987;317:1098.

