# Efficacy and tolerance of methotrexate in plaque psoriasis. A prospective real-life multicenter study in France

A. Tournier [a], A. Khemis [b], F. Maccari [c], Z. Reguiai [d], E. Bégon [e], A.-C. Fougerousse [c], M. Amy de la Breteque [a], N. Beneton [f], J. Parier [g], T. Boyé [h], M. Avenel-Audran [i], C. Girard [j], V. Pallure [k], J.-L. Perrot [l], M. Bastien [m], E. Mahé [a], A. Beauchet [n], et le GEM Resopso

[a] Centre Hospitalier Victor Dupouy, Argenteuil; [b] Hôpital Archet 2, Nice; [c] Hôpital d'Instruction des Armées Bégin, Saint-Mandé; [d] Hôpital Robert-Debré, Reims; [e] Hôpital René Dubos, Pontoise; [f] Centre Hospitalier, Le Mans; [g] La Varenne-Saint-Hilaire; [h] Hôpital d'Instruction des armées Saint-Anne, Toulon; [i] Centre Hospitalier Universitaire, Angers; [j] Centre Hospitalier Universitaire, Montpellier; [k] Centre Hospitalier, Perpignan; [l] Centre Hospitalier Universitaire, Saint-Priest-en-Jarez; [m] Joinville-Le-Pont; [n] CHU Ambroise Paré, Boulogne-Billancourt, France

**Introduction**. Methotrexate (MTX) is a major systemic treatment of moderate-to-severe plaque psoriasis. A randomized trial has recently been published evaluating a single (17.5mg) weekly dosage, but few prospective real-life data are available. The objective of this study was to evaluate prospectively the effectiveness of MTX in real life. The secondary objective were to evaluate the predictive parameters of treatment efficacy, and the frequency of adverse events.

**Material and methods**. A prospective cohort by consecutive inclusions in 25 centers members of the GEM RESOPSO included all adults with plaque psoriasis who were initiated MTX treatment. The criterion of effectiveness was obtaining a PASI75 at week (W) 12/16. Impact of demographic data, psoriasis characteristics (duration, topography, rheumatism), dosage (W12/16 dosage, cumulative dose after 4 weeks), and mode of administration (subcutaneous vs. oral, the concomitant use of folic acid) on efficacy was evaluated. Intent-to-treat (ITT) and per-protocol (PP) analyses were performed.

**Results**. 256 patients (F/H: 105/151; mean age: 45.0 years; rheumatism: 12.6%) with plaque psoriasis have been included. 99 patients have not been analyzed at W12/16 (16 because of inefficacy, 16 because of intolerance, 56 lost to follow-up or with missing data). A PASI 75 was obtained in 98 patients, with an efficacy rate of 38.3% in ITT and 58.3% in PP analysis. In ITT analysis (Table 1), the previous non-use of cyclosporine (p = 0.01) and the cumulative dose of MTX> 60 mg after 4 weeks (p <0.0001) were associated with a higher PASI75 level. In PP analysis (Table 2), only the previous non-use of cyclosporine (p = 0.0009) was associated with a higher PASI75 level. Neither the characteristics of the patients (including body mass index), the clinical aspects of psoriasis, the mode of administration, nor the folic acid combination or the W12/16 dose were associated with an increase of PASI75. Adverse events were reported by 34.8% of patients (Table 3). These were mainly digestive disorders (nausea, abdominal pain), asthenia and moderate cytolysis.

**Table 1**. Intention-to-Treat Analysis

| | All n=256 | < PASI75 n=158 | ≥ PASI75 n=98 | p |
|---|---|---|---|---|
| Sex, female | 105 (41,0%) | 62 (39,5%) | 43 (43,9) | 0,58 |
| Age (years) | 45,0 ± 14,7 | 44,7 ± 14,5 | 45,0 ± 15,0 | 0,87 |
| Body-mass-index (kg/m²) | 26,6 ± 5,8 | 26,8 ± 5,8 | 26,1 ± 5,8 | 0,36 |
| Obesity (BMI > 30) | 54 (21,1) | 36 (23,8) | 18 (18,4) | 0,32 |
| Smoking | 136 (53,1) | 81 (51,3) | 55 (56,1) | 0,45 |
| Alcohol consumption | 54 (21,1) | 32 (20,2) | 22 (22,5) | 0,67 |
| Psoriasis duration (years) | 14,6 ± 12,2 | 15,6 ± 11,6 | 14,1 ± 13,2 | 0,38 |
| Psoriatic arthritis | 32 (12,5) | 17 (10,8) | 15 (15,3) | 0,31 |
| Baseline PASI | 13,1 ± 7,8 | 12,8 ± 7,0 | 14,8 ± 8,4 | 0,05 |
| Baseline DLQI | 12,8 ± 6,2 | 12,6 ± 6,1 | 13,0 ± 6,4 | 0,73 |
| Baseline topography of psoriasis | | | | |
| scalp | 203 (79,3) | 120 (75,9) | 83 (84,7) | 0,09 |
| nails | 97 (37,9) | 62 (39,2) | 35 (35,7) | 0,57 |
| folds | 53 (20,7) | 30 (19,0) | 23 (23,5) | 0,39 |
| genital | 74 (28,9) | 41 (25,9) | 33 (33,7) | 0,18 |
| Previous treatment | | | | |
| phototherapy | 128 (71,1) | 75 (47,5) | 53 (54,1) | 0,30 |
| cyclosporine | 26 (10,2) | 22 (13,9) | 4 (4,1) | 0,01 |
| retinoids | 65 (25,4) | 40 (25,3) | 25 (25,5) | 0,97 |
| methotrexate | 10 (3,9) | 7 (2,7) | 3 (1,8) | |
| biological | 6 (2,3) | 3 (1,8) | 3 (1,8) | |
| Cumulative dose W0-W4* | 48,9 ± 23,1 | 42,0 ± 24,5 | 60,1 ± 15,0 | <0,0001 |
| Cumulative dose W0-W4* | | | | |
| 25-40 mg | 69 (27,0%) | 61 (38,6) | 8 (8,2) | <0,0001 |
| 45-55 mg | 62 (24,2%) | 34 (21,5) | 28 (28,6) | |
| 60-75 mg | 125 (48,8%) | 63 (39,9) | 62 (63,2) | |
| Mean dose at W4 | 16,5 ± 3,3 | 16,3 ± 3,4 | 16,7 ± 3,2 | 0,35 |
| Dose at W4 < 20 mg | 134 (66,0) | 72 (67,3) | 62 (64,6) | 0,80 |
| Assessment dose** | 16,3 ± 3,1 | 16,7 ± 3,5 | 16,5 ± 3,3 | 0,57 |
| Assessment dose < 20 mg** | 200 (78.1) | 133 (84.2) | 67 (68,4) | 0,005 |
| Oral administration | 212 (82,8) | 131 (82,9) | 81 (82,6) | 0,11 |
| Acid folic supplementation | 231 (90,2) | 143 (90,5) | 88 (89,8) | 0,31 |
| Adverse event before W12/W16 | 89 (34,8) | 51 (32,3) | 38 (38,8) | 0,29 |

Data are n (%) and mean ± standard deviation. BMI : Body Mass Index ; W : week ; AE : adverse event ; PASI : *Psoriasis Area Severity Index* ; DLQI : *Dermatology Quality of Life Index*
* = $1^{st}$ + $2^{nd}$ + $3^{rd}$ + $4^{th}$ dose of methotrexate
** dose of methotrexate at week12 or week16

**Table 2**. Per-protocol analysis

| | All n=168 | < PASI75 n=70 | ≥ PASI75 n=98 | p |
|---|---|---|---|---|
| Sex, female | 72 (42,9) | 29 (41,4) | 43 (43,9) | 0,75 |
| Age (years) | 46,0 ± 15,5 | 47,3 ± 16,3 | 45,0 ± 15,0 | 0,34 |
| Body-mass-index (kg/m²) | 26,4 ± 5,7 | 26,8 ± 5,7 | 26,1 ± 5,8 | 0,49 |
| Obesity (BMI > 30) | 33 (19,6) | 15 (21,4) | 18 (18,4) | 0,55 |
| Smoking | 98 (58,3) | 43 (61,4) | 55 (56,1) | 0,49 |
| Alcohol consumption | 42 (25,0) | 20 (28,6) | 22 (22,5) | 0,36 |
| Psoriasis duration (years) | 14,6 ± 12,7 | 16,1 ± 12,1 | 14,1 ± 13,2 | 0,32 |
| Psoriatic arthritis | 20 (11,9) | 5 (7,1) | 15 (15,3) | 0,11 |
| Baseline PASI | 14,0 ± 7,5 | 13,2 ± 7,4 | 14,8 ± 8,4 | 0,21 |
| Baseline DLQI | 12,7 ± 6,6 | 12,3 ± 6,9 | 13,0 ± 6,4 | 0,61 |
| Baseline topography of psoriasis | | | | |
| scalp | 138 (82,1) | 55 (78,6) | 83 (84,7) | 0,31 |
| nails | 63 (37,5) | 28 (40,0) | 35 (35,7) | 0,57 |
| folds | 37 (22,0) | 14 (20,0) | 23 (23,5) | 0,59 |
| genital | 52 (31,0) | 19 (27,1) | 33 (33,7) | 0,37 |
| Previous treatment | | | | |
| phototherapy | 88 (52,3) | 35 (50,0) | 53 (54,1) | 0,60 |
| cyclosporine | 15 (8,9) | 11 (15,7) | 4 (4,1) | 0,009 |
| retinoids | 41 (24,4) | 16 (22,8) | 25 (25,5) | 0,69 |
| methotrexate | 6 (3,6) | 3 (4,3) | 3 (3,1) | - |
| biological | 5 (3,0) | 2 (2,9) | 3 (3,1) | - |
| Cumulative dose W0-W4* | 58.3 ± 14.1 | 55,8 ± 12,4 | 60,1 ± 15,0 | 0,047 |
| Cumulative dose W0-W4* | | | | |
| 25-40 mg | 16 (9,5%) | 8 (11,4) | 8 (8,2) | 0,66 |
| 45-55 mg | 50 (29,8%) | 22 (31,4) | 28 (28,6) | |
| 60-75 mg | 102 (60,7%) | 40 (57,2) | 62 (63,2) | |
| Mean dose at W4 | 16.2 ± 3.9 | 16,0 ± 3,9 | 16,4 ± 4,0 | 0,51 |
| Dose at W4 < 20 mg | 112 (66,7%) | 48 (68,6) | 64 (65,3) | 0,66 |
| Assessment dose** | 16,5 ± 3,3 | 16,3 ± 3,1 | 16,7 ± 3,5 | 0,60 |
| Assessment dose < 20 mg** | 114 (67,9) | 47 (67,1) | 67 (68,4) | 0,87 |
| Oral administration | 137 (81,5) | 56 (80,0) | 81 (82,6) | 0,81 |
| Acid folic supplementation | 154 (91,7) | 66 (94,3) | 88 (89,8) | 0,45 |
| Adverse event before W12/W16 | 72 (42,9) | 34 (48,6) | 38 (38,8) | 0,21 |

Data are n (%) or mean ± standard deviation. BMI : Body Mass Index ; W : week ; AE : adverse event ; PASI : *Psoriasis Area Severity Index* ; DLQI : *Dermatology Quality of Life Index*
* = $1^{st}$ + $2^{nd}$ + $3^{rd}$ + $4^{th}$ dose of methotrexate
** dose of methotrexate at week12 or week16

**Table 3**. Adverse events

| | |
|---|---|
| Adverse events (except serious adverse event) | |
| Asthenia | 49 (19,1) |
| Gastrointestinal disorders (abdominal pain, nausea, …) | 38 (14,8) |
| Hepatic cytolysis (transaminases < 5 ULN ) | 20 (7,8) |
| Weight loss | 5 (2,0) |
| Infections | 5 (2,0) |
| Anaemia | 2 (0,8) |
| Serious adverse events | |
| Malaise with loss of consciousness | 1 (0,4) |
| Pneumonia (infectious) | 1 (0,4) |
| Hypersensitivity pneumonitis | 1 (0,4) |

Data are n (%). ULN=upper limit of normal

**Discussion**. The efficacy of MTX in plaque psoriasis in this real-life study of 256 patients is consistent with literature data including the recently published randomized trial (41% of PASI75). The weight of the patient, the route of administration, or the combination with folic acid don't modify this rate. The previous non-use of cyclosporine would be associated with better efficacy without clear explanation. The initial dosage (high dose of the first month) would be associated with better W12/S16 efficacy.

**Disclosures**: AK: Abbvie, Amgen, Celgene, Janssen, MSD, Novartis, Pfizer, UCB Pharma ; FM: Abbvie, Janssen-Cilag, Leo Pharma; ZR: Abbvie, Janssen Cilag, Novartis, Pfizer ; EB : Janssen Cilag ; ACF: Pfizer, Abbvie, Celgene, Novartis, Janssen-Cilag, Leo Pharma, Genevrier, Lilly; MAB: Novartis, Janssen-Cilag; NB: Abbvie, Celgene, Janssen-Cilag, Leo Pharma, Lilly, Novartis, Pfizer; JP: Janssen-Cilag, Novartis, Celgene, Léo Pharma; TB: Abbvie, Celgene, Janssen Cilag, Leo Pharma, Novartis, Pfizer; MAA: Abbvie, Celgène, Génévrier, Janssen Cilag, Léo Pharma, Novartis; CG: Abbvie; JLP: Abbvie, Janssen Cilag, MSD, Novartis; MB: Novartis; EM: Abbvie, Boehringer Ingelheim, Astra Zeneca, Amgen, Celgene, Janssen-Cilag, Leo Pharma, Pfizer, Novartis.
AT, VP, AB: none,