Topiramate in migraine prevention - Analysis of the core phase of an open-label, multi-centre, single treatment study in Germany

Göbel H[1]; Brand J[2]; Bornhövd K[3]; Schmitt L[4] for the TOPMAT-MIG-3004 Study Group
[1]Schmerzklinik, Kiel, [2]Migräneklinik, Königstein, [3,4]Praxis für Neurologie und Spezielle Schmerztherapie, Hamburg

OBJECTIVE

- About 25 % of migraine patients suffer from a high frequency of monthly migraine attacks (≥ 6 per month).[1]
- A high frequency of monthly migraine attacks can cause a high intake of acute headache medication and thus lead to a progression of medication overuse headache.[2] A prevention of migraine attacks can reduce headache frequency and thus avoide medication overuse.
- Efficacy and tolerability of Topiramate in migraine prevention has been demonstrated in a large randomized, placebo-controlled study program including more than 1500 patients.[3, 4, 5]
- The aim of this open-label non-comparative multi-centre trial (TOP-MAT-MIG-3004) was to investigate if Topiramate (TPM) is effective and well tolerated in the reduction of migraine attacks in patients with a diagnosis of episodic migraine according to IHS-criteria[6] allowing a flexible dose titration (between 50-200mg/d) according to patient needs.

METHODS

Study design

- Treatment was started generally with 25mg/d TPM.
- If required, daily doses were increased in weekly increments of 25mg/d up to individual maintenance doses.
- Treatments were maintained with daily doses between 50-200mg/d. During the last 4 weeks of the treatment phase (week 20-24) the dose was kept stable.

Main Inclusion criteria

- Patients aged 18 to 80 years with a diagnosis of episodic migraine according to IHS criteria[6] for at least one year.
- Patients with at least 3 migraine attacks/ 4 weeks but not more than 15 migraine days/ month during the prospective baseline phase.

Main Exclusion criteria

- More than three failures (due to a lack of efficacy) of adequate previous regimens of migraine prophylactic medications in the last year prior to trial entry.
- Medication overuse headache or any other primary or secondary headache according to the IHS criteria (except for infrequent tension type headache).[6]
- Beck Depression Inventory >18

Efficacy parameters

- Patients were given a diary to report migraine days or attacks and other migraine symptomes as well as intake of acute headache medication.
- Primary efficacy parameter:
  - Change in the number of migraine days from the baseline period to the last 4 weeks of the treatment period.
- Secondary efficacy parameters:
  - Change in the number of migraine periods and attacks from the baseline period compared to the last 4 weeks of treatment period.
  - Responder-rates (e.g. 50%- Responder-rate = Patients who had at least a 50% reduction in migraine frequency).
  - Change in the number of days with intake of acute headache medication per month.
  - Changes in quality of life (QoL) were evaluated using validated questionnaires:
    - MIDAS (at week 0, 12 and 24) and HIT-6 (at week 0, 8 and 24):
      - Questions about migraine specific symptoms. Lower scores = better QoL.
    - Patient Questionnaire:
      - Assessment of preventive therapy: Effectiveness (Question1), Tolerability (Question 2) and overall (Question 3).

Safety parameters

- Tolerability and safety were recorded by reporting adverse events (AE) and safety parameters (e.g. body weight).

RESULTS

Study population

- Of 403 screened patients 364 received Topiramate at least once (Safety-population). 360 were included in ITT-population. For demographics s. Tab.1.

Tab. 1 Demographics of ITT-population

Sex	f: 87.8 % m: 12.2 %	n = 316 n = 44
Age	Ø 43.7 Years [18 – 75 Y.]	
Body hight	Ø 168 cm [150 – 199 cm]	
Body weight	Ø 72.0 kg [4 – 154 kg]	
BMI	Ø 25,6 [16,9 – 52]	

- Patients, aged 18 to 80 years with a diagnosis of episodic migraine according to IHS-criteria, suffered on average for approximately five years from at least three migraine attacks per month.
- 60.6 % of the patients suffered from migraine without aura, 39.4 % reported migraine with aura symptoms.
- Most frequently previous preventive treatments: Beta-blockers (40.6 %) and Calcium channel blockers (21.1 %).
- The average Topiramate-dose was 90±43 mg/d.

Effectiveness

- The mean number of migraine days/28 days decreased significantly from 8.3±3.0 to 4.3±3.0 after 24 weeks (Fig. 1).
- In 54.55 % of the patients treated for 24 weeks the migraine frequency reduced about at least 50 %. A reduction of migraine frequency about at least 90 % was seen in 13.4 % of the patients after 24 weeks (Fig. 2).
- Mean number of days with intake of acute headache medication decreased from 6.9±3.0 to 3.7±2.8 in patients treated for 24 weeks (Fig. 3).

Fig.1 Change in the number of migraine days after 24 weeks (ITT)

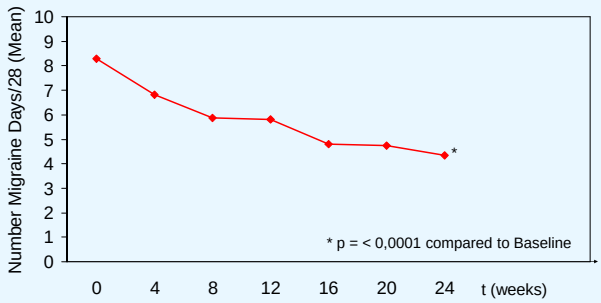


Fig. 2 Responder-rates after 24 weeks (ITT)

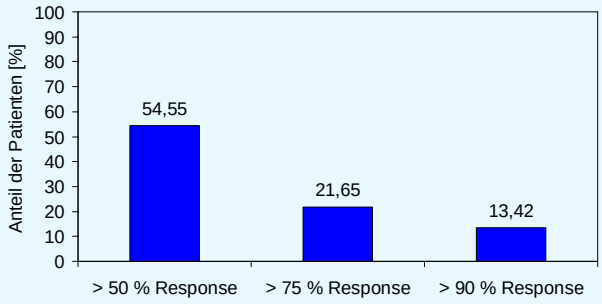
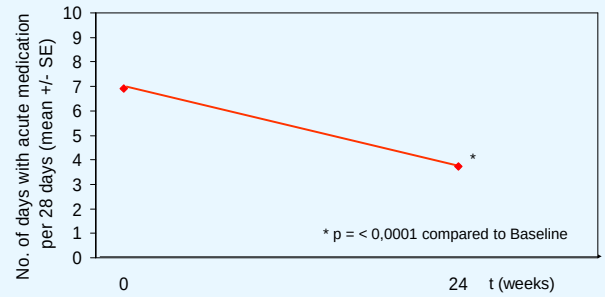


Fig. 3 Change in days/months with intake of acute headache mediacation (ITT)

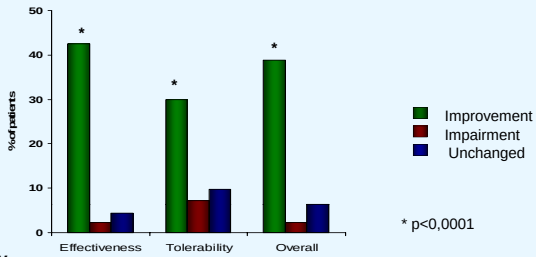


Quality of Life

QoL and treatment-satisfaction improved significantly in patients treated for 24 weeks.

- HIT-6:
  - Both the scores for all questions and the total score improved significantly (p<0.0001).
  - The total score improved in 70.8% of the patients, on average from 65,1 to 55,7.
- MIDAS:
  - Both the scores for all questions and the total score improved significantly (p<0.0001).
  - The total score decreased compared to baseline (improvement), on average from 42.5 to 17.0.
- Patient questionnaire on treatment satisfaction:
  - The vast majority of patients in whom a comparison was possible preferred prophylaxis with Topiramate.
  - Improvements were significant for all questions (p<0,0001) (Fig. 4).

Fig. 4. Improvement of treatment satisfaction (ITT)



Safety

- 321 Patients (88.2%) in the safety analysis reported at least one AE during the six month core phase.
- The most frequent AE of all AE present in >10% of patients were paresthesia (45.6%), fatigue (17.0%), nausea (14,6%), dizziness (12,9%), body weight decrease (12,4%) and viral infection (10,7%).
- 42 serious AEs were reported by 27 patients after the baseline phase.
- The observed AEs and serious AEs with at least a possible causality, except "haematoma" and "syncope", which were processed as SUSAR, are in accordance with the known safety profile.
- No clinically relevant changes in safety-parameters were observed.

Conclusions

- Topiramate, using a flexible dose-regime, is well tolerated and effective in reducing migraine days and intake of acute medication.
- In addition, quality of life and treatment-satisfaction improved significantly.
- These data are in line with recent controlled Topiramate studies which demonstrated good efficacy and tolerability.

LITERATUR
1. Dahlöf C, Linde M. One-year prevalence of migraine in Sweden: a population based study in adults. Cephalalgia 2001; 21:664-671
2. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology 2001; 57:1694-1698
3. Brandes JL et al. JAMA 2004; 291:965-973
4. Diener HC et al. J Neurol 2004; 251:943
5. Silberstein SD et al. Arch Neurol 2004; 61:490
6. The international Classification of Headache Disorders, 2nd Edition (ICHD-II). Cephalalgia 2004; 24 (Suppl. 1):1-195

IHC 2007, Stockholm, Sweden