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INSIDER
Investigator-Initiated Trials in Rheumatology



OA TREAT:

Hydroxychloroquine in Patients with Inflammatory and Erosive Osteoarthritis of the Hands

– an ongoing randomized controlled trial

Pascal Klaus

Department for Rheumatology and Clinical Immunology

Charité – Universitätsmedizin Berlin
Campus Mitte
Berlin, Germany

Pharmacovigilance and Clinical Trials, London, 08/12/2015

OA TREAT



investigator-initiated
based on a grant of the
German Ministry of Science

- prospective
- randomised
- double-blind and
- placebo-controlled
- clinical trial
- of hydroxychloroquine (HCQ)
- in patients with
- erosive inflammatory osteoarthritis of the hands

- **acronym: OA TREAT**

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Participating Prüfzentren



Currently 44 sites across Germany (aim: 60 sites)

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Agenda

- Background
  - Osteoarthritis
  - Hydroxychloroquine
- Trial design OA TREAT
- Challenges


16.03.2009–12.12.2009

DB

Abfahrt *Departure Départ* **Pforzheim-Weißenstein**

Zeit Time	Zug Train	Richtung Direction	Gleis Track
4:00 – 6:00			
4:51	RB 22241	Unterreichenbach 4:57 ⊙ Bad Liebenzell 5:04 – Hirsau 5:09 – Calw 5:12 – Wildberg 5:23 – Nagold 5:35 – Hochdorf 5:47 – **Horb 6:00**	1
5:59	RB 22240	PF-Brötzingen 6:02 ⊙ **Pforzheim Hbf 6:07**	1
6:25	RB 22243	Unterreichenbach 6:31 ⊙ Bad Liebenzell 6:39 – Hirsau 6:43 – Calw 6:46 – Wildberg 6:59 – Nagold 7:07 – Hochdorf 7:21 – **Horb 7:35** X außer Sa vom 9. bis 17. Apr, 25. Mai bis 5. Jun; 30. Jul bis 11. Sep; 26. bis 30. Okt nur bis **Nagold**	1
6:26	RB 22280	PF-Brötzingen 6:29 ⊙ **Pforzheim Hbf 6:34**	2
6:43	RB 22242	PF-Brötzingen 6:46 ⊙ **Pforzheim Hbf 6:51**	1
6:45	RB 22245	Unterreichenbach 6:51 ⊙ Bad Liebenzell 7:00 – Hirsau 7:11 – Calw 7:15 – Wildberg 7:33 – Nagold 7:41 – Hochdorf 7:52 – **Horb 8:05**	1
6:58	RB 22244	PF-Brötzingen 7:01 ⊙ **Pforzheim Hbf 7:06**	1
7:00 – 8:00			
7:18	RB 22246	PF-Brötzingen 7:21 – **Pforzheim Hbf 7:26** ⊙	1
7:30	RB 22281	Unterreichenbach 7:36 ⊙ Bad Liebenzell 7:43 – Hirsau 7:48 – Calw 7:51 – Wildberg 8:04 – **Nagold 8:12**	1
7:58	RB 22412	Unterreichenbach 8:04 ⊙ Bad Liebenzell 8:13 – Hirsau 8:18 – Calw 8:21 – Wildberg 8:35 – Nagold 8:43 – Hochdorf 8:52 – Horb 9:05 – **Tübingen Hbf 9:54**	1
7:59	RB 22248	PF-Brötzingen 8:02 ⊙ **Pforzheim Hbf 8:08**	2
8:28	RB 22282	PF-Brötzingen 8:31 ⊙ **Pforzheim Hbf 8:36**	1
8:57	RB 22251 RB 22253	Unterreichenbach 9:02 ⊙ Bad Liebenzell 9:10 – Hirsau 9:19 – Calw 9:22 – Wildberg 9:35 – Nagold 9:43 – Hochdorf 9:52 – **Horb 10:05**	1
8:58	RB 22256	PF-Brötzingen 9:01 ⊙ **Pforzheim Hbf 9:07**	2
9:00 – 11:00			
9:28	RB 22284	PF-Brötzingen 9:31 ⊙ **Pforzheim Hbf 9:37**	1
9:57	RB 22416	Unterreichenbach 10:03 ⊙ Bad Liebenzell 10:11 – Hirsau 10:18 – Calw 10:21 – Wildberg 10:35 – Nagold 10:43 – Hochdorf 10:52 – Horb 11:05 – **Tübingen Hbf 11:55**	1
9:58	RB 22407	PF-Brötzingen 10:01 ⊙ **Pforzheim Hbf 10:07**	1
10:57	RB 22255 RB 22257	Unterreichenbach 11:02 ⊙ Bad Liebenzell 11:10 – Hirsau 11:19 – Calw 11:22 – Wildberg 11:35 – Nagold 11:43 – Hochdorf 11:52 – **Horb 12:05**	1
10:58	RB 22258	PF-Brötzingen 11:01 ⊙ **Pforzheim Hbf 11:07**	2
11:26	RB 22283	Unterreichenbach 11:32 ⊙ Bad Liebenzell 11:39 – Hirsau 11:49 – Calw 11:52 – Wildberg 12:05 – **Nagold 12:13**	1
11:57	RB 22420	Unterreichenbach 12:03 ⊙ Bad Liebenzell 12:11 – Hirsau 12:18 – Calw 12:21 – Wildberg 12:35 – Nagold 12:43 – Hochdorf 12:52 – Horb 13:05 – **Tübingen Hbf 13:55**	1
11:58	RB 22411	PF-Brötzingen 12:01 ⊙ **Pforzheim Hbf 12:07**	2
12:00 – 13:00			
12:26	RB 22285	Unterreichenbach 12:32 ⊙ Bad Liebenzell 12:39 – Hirsau 12:49 – Calw 12:52 – Wildberg 13:05 – **Nagold 13:13**	1
12:57	RB 22259 RB 22261	Unterreichenbach 13:03 ⊙ Bad Liebenzell 13:13 – Hirsau 13:19 – Calw 13:22 – Wildberg 13:35 – Nagold 13:43 – Hochdorf 13:52 – **Horb 14:05**	1
12:58	RB 22262	PF-Brötzingen 13:01 ⊙ **Pforzheim Hbf 13:07**	2
13:28	RB 22287	Unterreichenbach 13:34 ⊙ Bad Liebenzell 13:43 – Hirsau 13:49 – Calw 13:52 – Wildberg 14:05 – **Nagold 14:13**	1
13:29	RB 22286	PF-Brötzingen 13:32 ⊙ **Pforzheim Hbf 13:37**	2
13:57	RB 22424	Unterreichenbach 14:03 ⊙ Bad Liebenzell 14:13 – Hirsau 14:18 – Calw 14:21 – Wildberg 14:35 – Nagold 14:43 – Hochdorf 14:52 – **Horb 15:05** Sa, ↑ **Tübingen Hbf 15:55**	1
13:58	RB 22415	PF-Brötzingen 14:01 ⊙ **Pforzheim Hbf 14:07**	2
14:00 – 15:00			
14:28	RB 22289	Unterreichenbach 14:34 ⊙ Bad Liebenzell 14:43 – Hirsau 14:49 – Calw 14:52 – Wildberg 15:05 – **Nagold 15:13**	1
14:29	RB 22288	PF-Brötzingen 14:32 ⊙ **Pforzheim Hbf 14:37**	2
14:57	RB 22263 RB 22265	Unterreichenbach 15:03 ⊙ Bad Liebenzell 15:13 – Hirsau 15:19 – Calw 15:22 – Wildberg 15:35 – Nagold 15:43 – Hochdorf 15:52 – **Horb 16:05**	1
14:58	RB 22266	PF-Brötzingen 15:01 ⊙ **Pforzheim Hbf 15:07**	2
15:28	RB 22291	Unterreichenbach 15:34 ⊙ Bad Liebenzell 15:43 – Hirsau 15:49 – Calw 15:52 – Wildberg 16:05 – **Nagold 16:13**	1
15:29	RB 22290	PF-Brötzingen 15:32 ⊙ **Pforzheim Hbf 15:37**	2
15:57	RB 22430	Unterreichenbach 16:03 ⊙ Bad Liebenzell 16:13 – Hirsau 16:18 – Calw 16:21 – Wildberg 16:35 – Nagold 16:43 – Hochdorf 16:52 – Horb 17:05 – **Tübingen Hbf 17:55**	1
15:58	RB 22423	PF-Brötzingen 16:01 ⊙ **Pforzheim Hbf 16:07**	2
16:00 – 17:00			
16:28	RB 22293	Unterreichenbach 16:34 ⊙ Bad Liebenzell 16:43 – Hirsau 16:49 – Calw 16:52 – Wildberg 17:05 – **Nagold 17:13**	1
16:29	RB 22292	PF-Brötzingen 16:32 ⊙ **Pforzheim Hbf 16:37**	2
16:57	RB 22267 RB 22269	Unterreichenbach 17:03 ⊙ Bad Liebenzell 17:13 – Hirsau 17:19 – Calw 17:22 – Wildberg 17:35 – Nagold 17:43 – Hochdorf 17:52 – **Horb 18:05**	1
16:58	RB 22270	PF-Brötzingen 17:01 ⊙ **Pforzheim Hbf 17:07**	2
17:28	RB 22295	Unterreichenbach 17:34 ⊙ Bad Liebenzell 17:43 – Hirsau 17:49 – Calw 17:52 – Wildberg 18:05 – Nagold 18:13 – Hochdorf 18:24 – **Horb 18:35**	1
17:29	RB 22294	PF-Brötzingen 17:32 ⊙ **Pforzheim Hbf 17:37**	2
17:57	RB 22436	Unterreichenbach 18:03 ⊙ Bad Liebenzell 18:13 – Hirsau 18:18 – Calw 18:21 – Wildberg 18:35 – Nagold 18:43 – Hochdorf 18:52 – Horb 19:05 – **Tübingen Hbf 19:54**	1
17:58	RB 22427	PF-Brötzingen 18:01 ⊙ **Pforzheim Hbf 18:07**	2
18:00 – 19:00			
18:28	RB 22297	Unterreichenbach 18:34 ⊙ Bad Liebenzell 18:43 – Hirsau 18:49 – Calw 18:52 – Wildberg 19:05 – Nagold 19:13 – Hochdorf 19:24 – **Horb 19:35**	1
18:29	RB 22296	PF-Brötzingen 18:32 ⊙ **Pforzheim Hbf 18:37**	2
18:57	RB 22271	Unterreichenbach 19:03 ⊙ Bad Liebenzell 19:13 – Hirsau 19:19 – Calw 19:22 – Wildberg 19:35 – Nagold 19:43 – Hochdorf 19:52 – **Horb 20:05**	1
18:58	RB 22274	PF-Brötzingen 19:01 ⊙ **Pforzheim Hbf 19:07**	2
19:57	RB 22440	Unterreichenbach 20:03 ⊙ Bad Liebenzell 20:13 – Hirsau 20:18 – Calw 20:21 – Wildberg 20:35 – Nagold 20:43 – Hochdorf 20:52 – Horb 21:05 – Tübingen Hbf 21:54 – **Reutlingen Hbf 22:19**	1
19:58	RB 22431	PF-Brötzingen 20:01 ⊙ **Pforzheim Hbf 20:06**	2
20:00 – 23:00			
20:57	RB 22273	Unterreichenbach 21:02 ⊙ Bad Liebenzell 21:10 – Hirsau 21:15 – Calw 21:18 – Wildberg 21:29 – Nagold 21:37 – Hochdorf 21:48 – **Horb 22:07**	1
20:58	RB 22276	PF-Brötzingen 21:01 ⊙ **Pforzheim Hbf 21:07**	2
21:49	RB 22275	Unterreichenbach 21:55 ⊙ Bad Liebenzell 22:03 – Hirsau 22:12 – Calw 22:14 – Wildberg 22:25 – Nagold 22:34 – Hochdorf 22:44 – **Horb 23:04**	1
22:59	RB 22278	PF-Brötzingen 23:02 ⊙ **Pforzheim Hbf 23:08**	1
23:56	RB 22277	Unterreichenbach 0:02 ⊙ Bad Liebenzell 0:09 – Hirsau 0:15 – Calw 0:18 – Wildberg 0:29 – Nagold 0:37 – Hochdorf 0:47 – **Horb 1:00** *auch 9., 13. Apr, 20., 21. Mai, 1., 10., 11. Jun	1
23:58	RB 22298	PF-Brötzingen 0:01 ⊙ **Pforzheim Hbf 0:06** *nicht 12. Apr, 31. Mai, auch 13. Apr, 21. Mai, 1., 11. Jun	2

Zeichenerklärung

Züge im Regional- und Nahverkehr

RB **Regionalbahn** nur 2.Kl

Symbole

⊙ bis hier sind alle Halte angegeben

Verkehrstage

Mo Montag - Monday - Lundi
Di Dienstag - Tuesday - Mardi
Mi Mittwoch - Wednesday - Mercredi
Do Donnerstag - Thursday - Jeudi
Fr Freitag - Friday - Vendredi
Sa Samstag - Saturday - Samedi
So Sonntag - Sunday - Dimanche
X an Werktagen - on workingdays - les jours ouvrables
† an Sonntagen und folgenden Feiertagen: Karfreitag (10.04.), Ostermontag (13.04.), Tag der Arbeit (01.05.), Christi Himmelfahrt (21.05.), Pfingstmontag (01.06.), Fronleichnam (11.06.), Tag der dt. Einheit (03.10.), Allerheiligen (01.11.)

Berichtigt werden nur die im Bahnhof Pforzheim-Weißenstein ausgehängten Pläne.

Angaben ohne Gewähr - Änderungen und Irrtümer vorbehalten.

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EROSIVE OSTEOARTHRITIS OF THE HANDS

Prevalence of HOA

- high prevalence of hand osteoarthritis (HOA)
- radiographic signs
  - > 80% of the elderly population
- symptomatic HOA
  - 5-20% of the elderly population



Dahaghin (Ann Rheum Dis 2005)

Dillon (Am J Phys Med Rehabil 2007)

Burden of Disease



- HOA often considered as „mild disease“
- burden of disease can be very high
    - strong pain
    - restricted function
    - reduced grip strength
    - aesthetic changes

Kloppenburg (Nat Rev Rheumatol 2012)

Erosive Hand OA (EOA)



- Subgroup of HOA, radiographic signs:
  - central erosions
  - collapse of the subchondral corticalis
- lower prevalence:
  - 3% of adults ≥ 55 Jahre
  - 10% of patients with symptomatic HOA

Kwok (Ann Rheum Dis 2011)



Punzi (Best Pract Res Clin Rheum 2010)

EOA



- unclear if
  - more severe form of HOA
  - or distinct disease with specific pathogenesis
- additionally pronounced inflammatory component
  - swelling
  - redness
  - hyperthermia of affected joints
  - occasionally systemic inflammation markers
  - Up-regulation of pro-inflammatory cytokines in synovia, cartilage und subchondral bone
- therefore also called „inflammatory OA“ or „erosive inflammatory OA“

Kwok (Ann Rheum Dis 2011)



EULAR RECOMMENDATIONS FOR THE TREATMENT OF HAND OSTEOARTHRITIS

Non-Pharmacologic Therapy



- EULAR recommendations name non-pharmacologic therapy options in first place
  - patient education
  - physiotherapeutical exercise
  - application of local warmth, e.g. paraffin bath
- lack of clinical studies
- therefore graded only as expert opinion

Zhang (Ann Rheum Dis 2007)

Topic NSAIDs / Capsaicin



- Metaanalysis on the use of topic NSAIDs
  - effective for pain therapy
  - effectivity comparable to oral NSAIDs
- topic capsaicin superior to placebo in two RCT considering clinical parameters

Lin (BMJ 2004)

Mccarthy (J Rheumatol 1992)

Schnitzer (Semin Arthritis Rheum 1994)

Paracetamol



- according to EULAR recommendations oral drug of first choice when effective
  - well tolerated
  - low costs
- used for decades for the treatment of HOA
- but: no placebo-controlled trials for HOA
- evidence extrapolated from studies on OA in other joints

Zhang (Ann Rheum Dis 2007)

NSAIDs / Coxibs



- Head-to-Head comparison NSAIDs/coxibs vs. paracetamol:
  NSAIDs/coxibs superior
- BUT:
  - gastrointestinal side effects
  - cardiovascular risk

Intraarticular Glucocorticoid Injections



- No improvement of symptoms in a placebo-controlled RCT with 40 patients
- Short-term improment of complaints in a small uncontrolled study
- Application limited for practical reasons
- Mostly applied for CMC I

Meenagh (Ann Rheum Dis 2004)

Joshi (J Rheumatol 2005)

Surgical Interventions



- Possible options:
  - Interposition arthroplasty
  - Osteotomy
  - Arthrodesis
- Very effective to treat complaints, but often associated with loss of function
- After failure of other therapeutic options
- Mostly limited to CMC I

Zhang (Ann Rheum Dis 2007)



PROBLEM:

Paracetamol and NSAID NOT effective

in many patients with EOA!!

Innovative Therapy Options



- Nuclear medical treatment
  - X-ray radiation, radiosynoviorthesis
- SYSADOA = symptomatic slow-acting drugs for OA
  - Chondroitinsulfate, glucosamine, avocado/soy bean extract
- DMOAD = disease-modifying osteoarthritis drugs
  - MMP inhibitors, bisphosphonates
- Biologicals used in RA



HYDROXYCHLOROQUINE

Chinabark Tree



- 1639: Countess of Cinchon
- wife of the Spanish vice king of Peru
- supposedly suffered from Malaria
- healed by a Jesuit father with an extract of the chinabark tree
- later her diaries were found: don‘t include evidence that she ever suffered from Malaria

Kalia (Dermatol Ther 2007)

Quinine

- Fact is that the bark of chinabark tree contains among others quinine
- 1894: first description of effectivity of quinine in cutaneous lupus erythematosus



Payne (Clin J 1894)

Malaria Prophylaxis in World War II

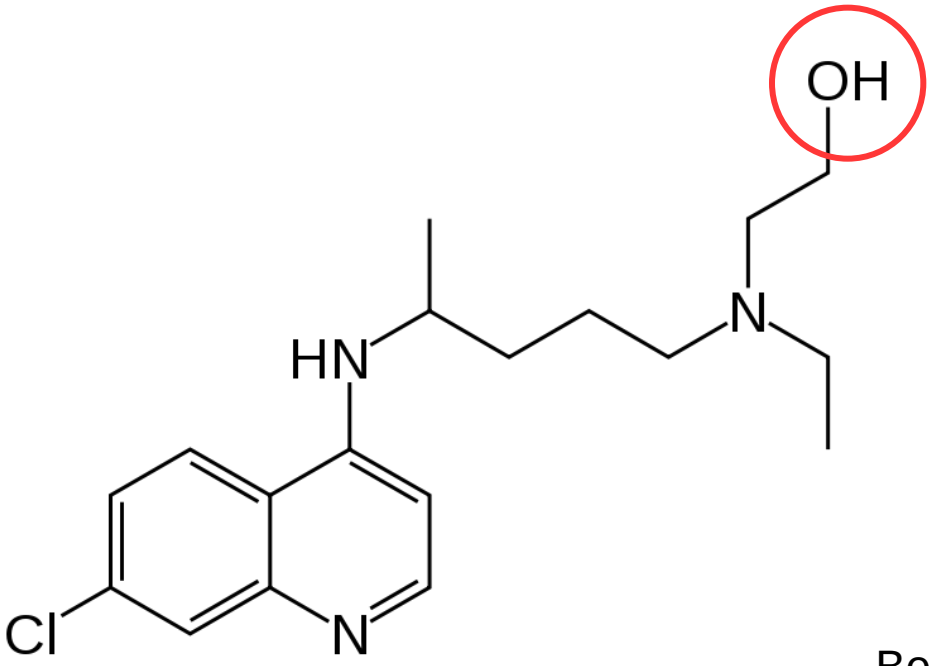


- Beginning of 20th century: Americans and Germans synthesize compounds related to quinine as part of their research for drugs against Malaria
- Chloroquine (CQ) most promising
- during World War II: millions of soldiers take quinine or CQ for malaria prophylaxis
- Side effect: Improvement of soldiers ‘ complaints with arthritis or skin changes

Ben-Zvi (Clinic Rev Allerg Immunol 2012)

Hydroxychloroquine (HCQ)

- first synthesized in 1955
- differs from CQ by a hydroxyl group
- reduced toxicity with maintained effectivity



Ben-Zvi (Clinic Rev Allerg Immunol 2012)

Side Effects



- diarrhea
- headache
- Dermatologic side effects, psoriasis
- nausea or vomiting
- Cardiomyopathy
- Hypersensitivity
- Hematologic side effects
- HCQ retinopathy

Ben-Zvi (Clinic Rev Allerg Immunol 2012)

Hydroxychloroquine in EOA



- Two retrospective studies
- One randomised, double-blind, placebo-controlled trial
- one randomised open trial (HCQ vs. Clodronat)

→ overall positive results, but very small cohort

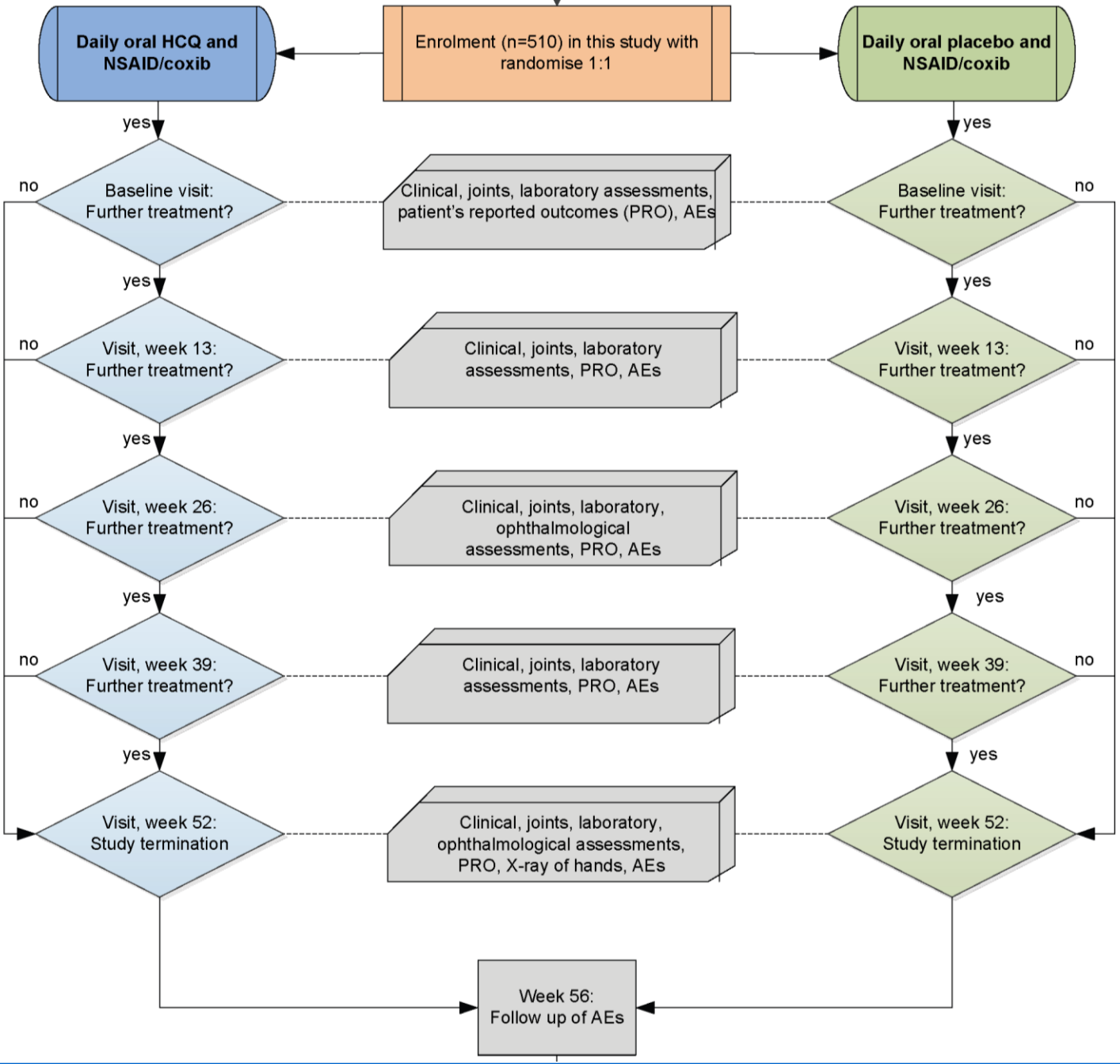
Robertson (Arthritis Rheum 1993)
Bryant (J Rheumatol 1995)
Punzi (J Rheumatol 1996)
Saviola (Mod Rheumatol 2012)



OA TREAT

– SYNOPSIS

Trial Overview



Primary Endpoints



- **co-primary clinical endpoint**
  - AUSCAN (Australian-Canadian OA Index) for pain and hand function in week 52
- **co-primary radiographic endpoint**
  - radiographic progression from Baseline to week 52
  - voluntary follow-up in week 104

Secondary Endpoints I



- Efficacy of HCQ (Baseline / W26 / W52)
  - AUSCAN Score
  - global patient assessment of disease activity,
  - global patient assessment of joint stiffness
  - global physician assessment of disease activity
- Pain, function, disability, quality of life (Baseline / W26 / W52)
  - HAQ
  - SF-36
  - SF-SACRAH
  - AUSCAN

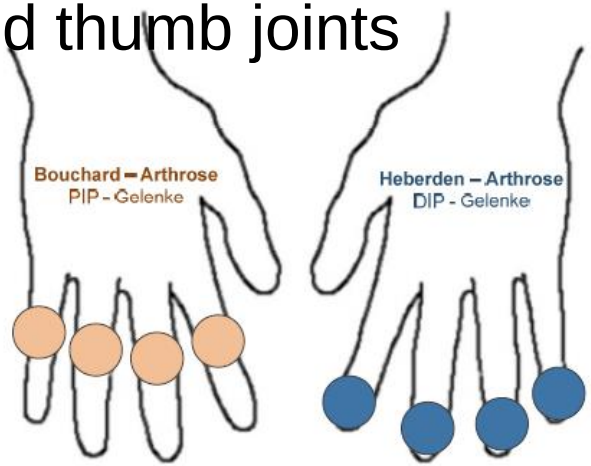
Secondary Endpoints II



- Inflammatory status (Baseline / W26 / W52)
  - joint pain
  - joint swelling
  - nocturnal pain
  - morning stiffness
  - local redness
  - CRP, ESR
- Use of standard medication during the past 7 days prior to each study visit
  - NSAIDs
  - Coxibs

Secondary Endpoints III

- joint status
  - number of painful joints upon palpation
  - number of joints with Heberden osteoarthritis
  - number of joints with Bouchard osteoarthritis
  - number of swollen (inflamed) joints (incl. rubor, dolor, calor)
  - number of joint deviations
  - number of subluxations of affected thumb joints
- safety parameters (adverse events)



Timeline



- First patient in
  - **November 2013**
- Current status of recruitment: ~100 patients
- Last patient out
  - **?**

Inclusion criteria



- Women and men
- age 40 to 80 years
- Clinical diagnosis of OA (ACR criteria)
  + inflammation in ≥ 3 finger joints
- Radiological diagnosis of OA (ACR criteria)
  + erosive joint changes
- necessity of regular treatment with analgetics/NSAIDs

Exclusion criteria I



- secondary OA (e.g. infectious arthritides, acromegaly, ochronosis, hemochromatosis, gout)
- other inflammatory joint disease
- psoriasis
- current or past treatment with HCQ due to hand OA
- pain syndrome of the upper extremity

Exclusion criteria II



- Contraindication against HCQ according to prescribing information
  - did not tolerate HCQ in the past
  - hypersensitivity against HCQ / related compounds
  - ophthalmologic diseases (e.g. retinopathy), where HCQ is contraindicated
  - lactose intolerance
  - liver or kidney insufficiency
  - other diseases with inacceptable risk
  - pregnancy and lactation period

Statistics



- modified intention-to- treat (all patients who received at least one dose are included)
- first primary hypothesis (AUSCAN scales pain and hand function at week 52): multiple endpoint test according to Läuter and O'Brian
- Only in case of a significant difference:
- second primary hypothesis (radiographic outcome at week 52): nonparametric ANCOVA
- secondary outcomes: parametric ANCOVA
- changes in co-use of NSAIDs/analgesics taken into consideration

Pharmacovigilance



- Second annual safety report 2015:
  - mostly gastroenterologic events
  - Upper respiratory infections
  - 6 SAEs (not related to HCQ or protocol)

Challenges



- Investigator-initiated trial
  - No support from pharma
  - Small team
  - Very limited resources
- Slow recruitment
  - EOA not as common as OA
  - Burden of disease high, but not high enough?
  - Placebo control
  - Long duration
  - Low priority for trial sites?

HCQ Trials – Update 2015



- HERO (UK)
  - 252 subjects with symptomatic hand OA
  - active treatment or placebo for 12 months
  - primary endpoint: change in hand pain between baseline and six months
  - Results 2015: no improvement in pain
- FABIO (Netherlands)
  - Similar design
  - Study completed, results to come

Kingsbury (Trials 2012, EULAR meeting 2015)
Lee (clinicaltrials.gov)

Chances

- Keep thinking positive!
- OA TREAT could make a valuable contribution for improved treatment of patients with EOA!



THANK YOU TO…

- Prof. G.-R. Burmester



- Dr. J. Detert



- Study group INSIDER and project partners

INSIDER
Investigator-Initiated Trials in Rheumatology

- participating TRIAL SITES
- participating PATIENTS



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THANK YOU FOR YOUR ATTENTION

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