Riscul infectios dupa administrarea de imunosupresoare in COVID-19

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Tocilizumab

- Actemra (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor used to treat moderate to severe rheumatoid arthritis in children and adults.

- Common side effects of Actemra include:
- unusual bleeding--nosebleeds, bleeding gums, abnormal vaginal bleeding, any bleeding that will not stop, blood in your urine or stools, coughing up blood or vomit that looks like coffee grounds;
- liver problems--loss of appetite, right-sided stomach pain, vomiting, tiredness, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes);
- signs of perforation (a hole or tear) in your stomach or intestines--fever, ongoing stomach pain, change in bowel habits.
- signs of infection--fever, chills, aches, tiredness, cough, skin sores, diarrhea, weight loss, burning when you urinate;

https://www.rxlist.com/actemra-side-effects-drug-center.htm#overview

- Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. Hepatitis B reactivation

- Higher incidence of neutropenia.
  - It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count,
    - In patients who develop an absolute neutrophil count less than 500 per mm3 treatment is not recommended.

https://www.rxlist.com/actemra-side-effects-drug-center.htm#overview

Serious Infections

The most common serious infections included

- herpes zoster, gastroenteritis
- pneumonia,
- urinary tract infection,
- cellulitis,
- diverticulitis,
- sepsis
- bacterial arthritis

Opportunistic infections,

- tuberculosis,
- cryptococcus, aspergillosis, candidiasis
- pneumocystosis

https://www.rxlist.com/actemra-side-effects-drug-center.htm#overview

- Do not administer ACTEMRA in patients with an active infection, including localized infections.

- The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:
  - with chronic or recurrent infection;
  - who have been exposed to tuberculosis;
  - with a history of serious or an opportunistic infection;
  - who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
  - with underlying conditions that may predispose them to infection.

https://www.rxlist.com/actemra-side-effects-drug-center.htm#overview

Anakinra

- Anakinra, a recombinant interleukin-1 receptor antagonist, is known to be effective in several hyperinflammatory disease

› Crit Care. 2020 Dec 10;24(1):688. doi: 10.1186/s13054-020-03364-w.

Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study

Emma J Kooistra [# 1 2], Nicole J B Waalders [# 1 2], Inge Grondman [2 3], Nico A F Janssen [2 3], Aline H de Nooijer [2 3], Mihai G Netea [2 3 4], Frank L van de Veerdonk [2 3], Esther Ewalds [5], Johannes G van der Hoeven [1 2], Matthijs Kox [# 1 2], Peter Pickkers [# 6 7], RCI-COVID-19 Study Group

Collaborators, Affiliations + expand

PMID: 33302991 PMCID: PMC7726611 DOI: 10.1186/s13054-020-03364-w

Free PMC article

Side effects

- Hematologic Common (1% to 10%):
  - Neutropenia, decreased total white blood cell count, decreased platelets
- Gastrointestinal
- Very common (10% or more):
  - Vomiting (14%)
- Common (1% to 10%):
  - Nausea, diarrhea, abdominal pain
- Hepatic
- Uncommon (0.1% to 1%):
  - Hepatic enzyme increased
- Nervous system
- Very common (10% or more):
  - Headache (12%)
- Musculoskeletal
- Common (1% to 10%):
  - Arthralgia
- Other
- Very common (10% or more):
  - Worsening of RA (19%), pyrexia (11%)
- Hypersensitivity
- Uncommon (0.1% to 1%):
  - Allergic reactions (including anaphylactic reactions), angioedema, urticaria, pruritus
- Oncologic
- Frequency not reported:
  - Increased rate of lymphoma

Infections

- Respiratory
- Very common (10% or more):
  - Upper respiratory tract infection (19%), nasopharyngitis (11%)
- Common (1% to 10%):
  - Sinusitis, bronchitis
- Genitourinary
- Common (1% to 10%):
  - Urinary tract infection

- Immunologic
- Common (1% to 10%):
  - Serious infections (primarily bacterial)
    - cellulitis,
    - pneumonia,
    - bone and joint infections),
    - influenza-like symptoms

Baricitinib

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

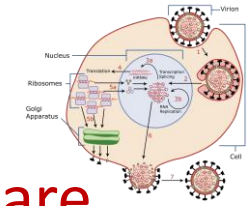
Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Andre C. Kalil, M.D., M.P.H., Thomas F. Patterson, M.D., Aneesh K. Mehta, M.D., Kay M. Tomashek, M.D., M.P.H., Cameron R. Wolfe, M.B., B.S., M.P.H., Varduhi Ghazaryan, M.D., Vincent C. Marconi, M.D., Guillermo M. Ruiz-Palacios, M.D., Lanny Hsieh, M.D., Susan Kline, M.D., Victor Tapson, M.D., Nicole M. Iovine, M.D., Ph.D., et al., for the ACTT-2 Study Group Members*

- Janus kinase inhibitor
- Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events.

- Ratele de raportate pentru Baricitinib în comparație cu placebo pentru reacții adverse la medicament vizând infecțiile au fost:
  - infecții ale tractului respirator superior (14,7 % față de 11,7 %),
  - infecții ale tractului urinar (3,4 % față de 2,7 %),
  - gastroenterită (1,6 % față de 0,8 %),
  - herpes simplex (1,8 % față de 0,7 %) și
  - herpes zoster (1,4 % față de 0,4 %).

Virusul Varicelo-zoosterian



- Reactivarea VZV este frecvent întâlnită în terapia cu imunosupresoare.
- Celulele CD4 + multifuncționale (IFN-y + IL-2 + TNF-a +) sunt implicate în supravegherea imună împotriva HZ latentă.

- Herpes zoster a fost raportat mai frecvent la pacienții cu vârsta ≥ 65 de ani care au fost tratați anterior cu terapii biologice.
- Reactivarea VZV, a fost raportată în studiile clinice efectuate de BARI.
  - Dintre cei 3492 de pacienti care au primit BARI in studiile clinice pentru tratamentul RA pana la 01 aprilie 2017,
    - 258 au avut dezvoltat HZ (7.38%)
      - 94,6% dintre cazuri au fost ușoare până la moderate în severitate
      - 8,5% din cazuri au fost multidermatomice;
      - 0 a avut o implicare viscerală

Genovese MC, Smolen JS, Takeuchi T, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 6 years: an updated integrated safety analysis Poster presented at: Annual Meeting of the American College of Rheumatology (ACR); October 20-24, 2018;

Table 2. Herpes Zoster by Patient Characteristic 6 Study Dataset Through 24 Weeks of Assigned Treatment[6]

	PBO + cDMARDs (N=1070)		BARI 4mg + cDMARDs (N=997)		BARI 4 mg vs PBO
	N	n (IR per 100 PY)	N	n (IR per 100 PY)	OR [95% CI]
Overall HZ cases reported as TEAEs	1070	4 (1.0)	997	18 (4.3)	4.6 [1.5, 13.6]
Age, years					
<50	378	1 (0.7)	336	3 (2.1)	2.9
≥50 and <65	519	2 (1.0)	462	9 (4.7)	5.0 [1.1, 23.4]
≥65	173	1 (1.5)	119	6 (7.2)	5.9 [0.7, 52.4]
Gender					
Male	208	1 (1.3)	203	4 (4.7)	4.3 [0.5, 40.9]
Female	862	3 (0.9)	794	14 (4.2)	4.7 [1.3, 16.6]
Background MTX					
Yes	967	3 (0.8)	903	14 (3.7)	4.7 [1.3, 16.3]
No	103	1 (2.5)	94	4 (10.6)	5.1 [0.5, 48.2]
Concomitant corticosteroid use					
Yes	610	4 (1.7)	538	9 (4.0)	2.5 [0.8, 8.3]
No	460	0	459	9 (4.7)	---
Time from RA diagnosis					
<5 years	376	1 (0.6)	380	7 (4.2)	7.6 [0.9, 63.9]
≥5 years	515	3 (1.4)	510	10 (4.4)	3.5 [1.0, 12.8]
Comorbid diabetes					
Yes	118	2 (4.4)	92	1 (2.6)	0.4
No	952	2 (0.6)	905	17 (4.5)	8.7 [2.0, 37.9]

Abbreviations: BARI = baricitinib; cDMARDs = conventional disease-modifying antirheumatic drugs; HZ = herpes zoster; IR = incidence rate; MTX = methotrexate; PBO = placebo; PY = patient years; RA = rheumatoid arthritis; TEAEs = treatment-emergent adverse events.

- **Dacă un pacient dezvoltă herpes zoster,**
  - tratamentul cu baricitinib trebuie întrerupt temporar până la rezolvarea episodului.
  - se inițiaza standarde de îngrijire (Acyclovir doze mari))
  - se monitorizeaza implicarea multi-dermatom sau alte dovezi de diseminare;
  - urmărirea până la recuperarea clinică a leziunilor cutanate

- **Vaccinarea VZV** este recomandată **anterior initierii terapiei cu baricitinib.** (> 30 de zile înainte de începerea terapiei)

- Vaccinurile vii nu trebuie administrate concomitent terapiei imunosuspresoare.

Genovese MC, Smolen JS, Takeuchi T, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 6 years: an updated integrated safety analysis Poster presented at: Annual Meeting of the American College of Rheumatology (ACR); October 20-24, 2018;

Vaccinare HZ

- Nu este indicata pentru prevenirea infecţiei primare (varicelă).
  - Prevenirea episoadelor de HZ
  - Prevenirea nevralgiei post-zosteriene
- **În timp ce vaccinarea HZ cu vaccin viu, atenuat este contraindicata la pacienții semnificativ imunocompromiși, inclusiv terapii imunosupresoare.**
- **Se indica vaccinul inactivat, recombinant.**

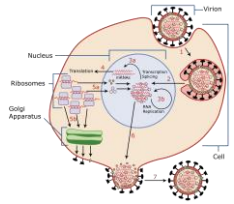
- 2 doze, administrate la 2 luni interval

Harvey MJ, Denton BT, Prosser LA, Hutton DW. Determining the optimal strategy for the herpes zoster vaccine in adults. *Vaccine*. 2018 Jul 18. doi: 10.1016/j.vaccine.2018.06.059. [Epub ahead of print]

Virusurile hepatitice B si C

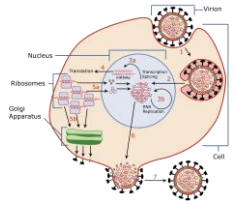
Patients with evidence of active hepatitis B or C infection were excluded from clinical trials.

Virusul hepatitic B



Reactivare VHB	
Definitie	- cresterea brusca , importanta a replicarii VHB (ADN-VHB) frecvent insotita de - cresterea TGP/TGO
Seroconversie inversa	Reaparitia AgHBs la o persoana AgHBs-, AcHBc+
Tratament imunosupresor	Poate să apară până la 12 luni după un tratament cu agenti imunosupresori
Tablou clinic	Variază de la asimptomatic la insuficienţă hepatică
PREVENIBILA PRIN PROFILAXIA ANTIVIRALA	

SCREENING VHB INAINTEA TERAPIEI IMUNOSUPRESOARE

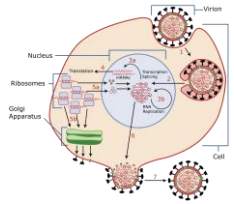


- Screeningul VHB este indicat în momentul prescrierii Baricitinib

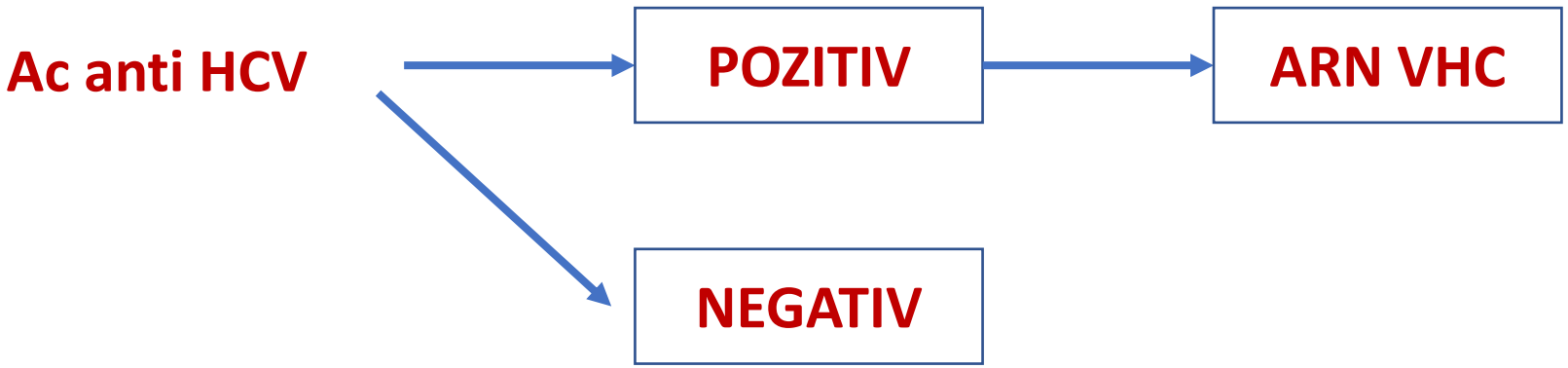
- **AgHBS**
  - **POZITIV** → **AgHBe, Ac antiHBs, ADN VHB**
  - **NEGATIV** → **Ac antiHBc**
    - **POZITIV** → **AgHBe, Ac antiHBs, ADN VHB**
    - **NEGATIV**

Asthana A, Lubel J. Reactivation of latent viruses after treatment with biological therapies Volume 2014:6 Pages 1—10 .

Virusul hepatitic C



- Screeningul VHC este indicat în momentul prescrierii Baricitinib



Asthana A, Lubel J. Reactivation of latent viruses after treatment with biological therapies Volume 2014:6 Pages 1—10 .