Ιδιαίτερο προφίλ ανοσοκατασταλμένων ασθενών:

Ασθενής σε θεραπεία με νεότερα φάρμακα μοριακής στόχευσης

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Επίκουρη Καθηγήτρια Αιματολογίας

Τμήμα Ιατρικής, Πανεπιστημίου Ιωαννίνων

Biological therapies

biological response modifiers

gene therapies

targeted therapies

Biological therapies

biological response modifiers

gene therapies

targeted therapies

- therapeutic monoclonal antibodies (mAbs)
  - Conjugated, bispecific
- small-molecule enzyme inhibitors
- proteasome inhibitors

Φάρμακα μοριακής στόχευσης
πόσο στοχευμένα;

- **Στοχεύουν:** κυτταροκίνες, διαλυτούς μεσολαβητές, μόρια επιφανείας και υποδοχείς, συστατικά ενδοκυττάριας σηματοδότησης που συμμετέχουν στον καρκίνο **ΑΛΛΑ** συχνά και σε σημαντικά στοιχεία φυσιολογικών διεργασίων όπως η φυσιολογική ομοιοστασία του ανοσοποιητικού και ο κυτταρικός κύκλος
- Η αναστολή τους μπορεί να οδηγήσει σε καταστολή της ανοσιακής απόκρισης και κίνδυνο λοίμωξης
  - Φυσική όσο και η επίκτητη ανοσία
  - απόκριση σε οξεία λοίμωξη όσο και σε χρόνια ή λανθάνουσα λοίμωξη

Στην καθημερινή κλινική πρακτική

… δύσκολη η απόλυτη (deterministic) συσχέτιση

Στην καθημερινή κλινική πρακτική

…δύσκολη η απόλυτη (deterministic) συσχέτιση

- Τη φύση και το στάδιο του υποκείμενου νοσήματος
- Την παρούσα ή προηγούμενη χορήγηση ανοσοκατασταλτικών
  - Ανάλογα πουρινών σε ΧΛΛ
  - Δεξαμεθαζόνη σε ΠΜ
  - Ανάγκη χορήγησης ανοκατασταλτικών λόγω ΑΕ π.χ. nivolumab or ipilimumab Διάρκεια θεραπείας – άθροιση δόσεων
    - Διαφορά στα ποσοστά λοιμώξεων με τη χορήγηση του anti-CD52 mAb alemtuzumb multiple sclerosis ή B-cell malignancy (η μέγιστη ετήσια δόση ποικίλει από 36 μέχρι 1080 mg αντίστοιχα)

Clinical Microbiology and Infection 24 (2018) 52–59

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction)

M. Fernández-Ruiz [1,2,*], Y. Meije [3], O. Manuel [4], H. Akan [5], J. Carratalà [2,6], J.M. Aguado [1,2], J. Delaloye [7]

2018

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH)

- summary of mechanism of action, approved indications and most common off-label uses
- theoretically **expected impact on the host's susceptibility** to infection
- **available evidence** (i.e. RCTs, postmarketing studies, case series and single case reports)
- suggested prevention and risk minimization strategies

Target molecule	Agents reviewed	Disease
BCR-ABL tyrosine kinase	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	CML
Bruton tyrosine kinase	Ibrutinib, acalabrutinib	CLL, Waldenström's, MCL
PI3K	Idelalisib, rigosertib, duvelisib	CLL, MDS
Bcl-2	venetoclax	CLL, AML
Janus kinases	Ruxolitinib	MF, PV
CD19	Blinatumomab	ALL
CD20	Rituximab, ofatumumab, obinutuzumab	NHL, CLL
CD22	inotuzumab ozogamicin	ALL
CD33	Gemtuzumab ozogamicin	AML
CD38	Daratumumab, isatuxumab	MM
Complement Factor C5	Eculizumab	PNH

Agents targeting lymphoid cells surface antigens: CD19, CD20

Anti-CD20 agents

Table 3
Main characteristics of different CD20-targeted agents

Generation	Drug	Type	Terminal half life	Clinical phase
First generation: murine or chimeric (human-mouse) antibodies	Rituximab	Chimeric	18–32 days depending on scheduling	Approved
	^{90}Y-ibritumomab	Murine, conjugated with a radioactive isotope	30 hours	Approved
Second generation: humanized or fully human antibodies developed with the purpose of reducing immunogenicity and improving efficacy	Ofatumumab[a]	Fully human	14 days	Approved
	Ocrelizumab	Humanized	26 days	Approved
	Veltuzumab	Humanized	10–15 days	Phase 2
	^{131}I-tositumomab	Fully human, conjugated with a radioactive isotope		Discontinued in 2013
Third generation: antibodies with an engineered Fc region to boost CDC and ADCC	Obinutuzumab	Humanized	28 days	Approved
	Ocaratuzumab	Humanized	19 days	Phase 3
	Ublituximab	Chimeric	6 days	Phase 2

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; Fc, crystallizable fraction.
[a] Induces cell lysis regardless of the level of expression of CD20, as well as rituximab-resistant CD20-positive cells.

Anti-CD20 agents

Τα πλασματοκύτταρα δεν εκφράζουν CD20 – οπότε δεν θα έπρεπε να επηρεάζεται η παραγωγή αντισωμάτων ωστόσο υπογαμμασφαιριναιμία έχει αναφερθεί μετά από πολλαπλές εγχύσεις

- **Anti-CD20 monoclonal antibodies impact immune response by modulating B-/T-cell interactions rather than directly affecting humoral immunity.**
  - B cells play a pivotal role in activating T cells through antigen presentation and cytokine release
  - B- cell depletion exerts a deleterious impact on the induction, maintenance and activation of cell-mediated immunity
- there are post-marketing reports associated with impaired cellular immunity
  - **Progressive multifocal leucoencephalopathy**
  - **Pneumocystis jirovecii pneumonia (PCP)**
  - **HCV** and **HBV** reactivation and dissemnated varicella-zoster virus (**VZV**) infection
- **Late onset neutropenia**

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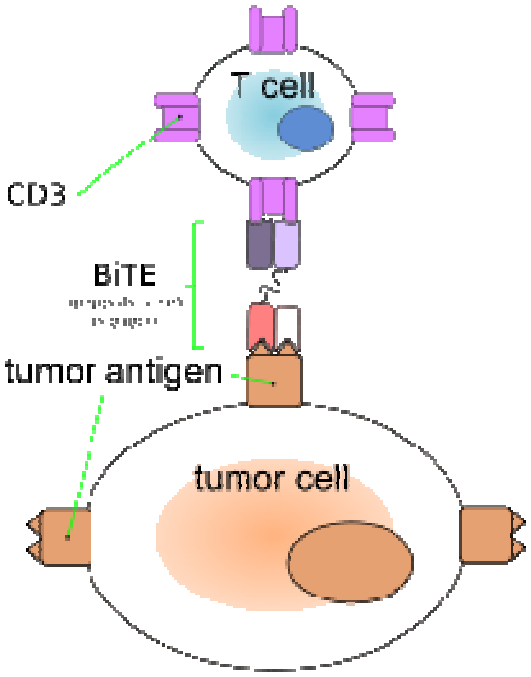
CD19-directed agents:
blinatumomab



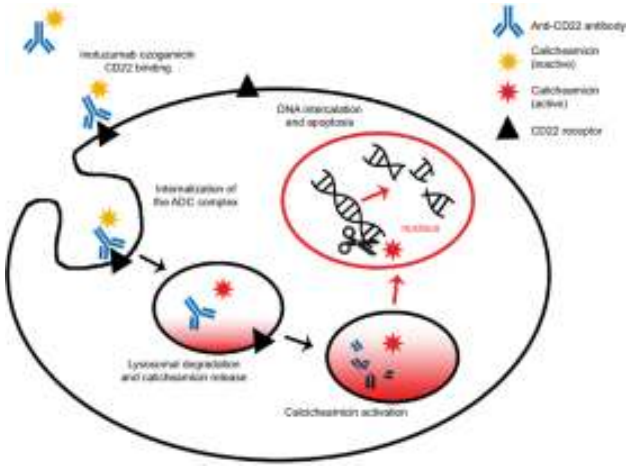
- The expression of CD19, which is almost exclusively restricted to B cells
  - all peripheral blood plasma cells
  - more than 50% of plasma cells in bone marrow
  - majority of B precursor ALL blast
- Depletion of normal B cells with the consequent **reduction in Ig level**
- In a phase 3 RCT the presence of IgG hypogammaglobulinaemia (HGG) occurred in **6%** of patients in the blinatumomab arm compared with **0.9%** of those treated with conventional chemotherapy
- **The rate of neutropenia with blinatumomab was lower** than with chemotherapy (38% versus 58%, respectively)
- **B-cell-dependent activation of T cells may be also affected** (as reported with anti-CD20 monoclonal antibodies)
- The **need for continuous 4-week intravenous** infusion responsible for a non-negligible rate of **catheter-associated infection**

Summary of infectious complications and possible management strategies for anti CD20 and anti CD19 agents

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for $HBsAg^{+}$/$HBsAg^{-}$ anti-HBc^{+})	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD19-targeted agents	Blinatumomab	No	Yes	Yes	Yes/yes	ND	Immunoglobulin replacement therapy if severe HGG
CD20-targeted agents	Rituximab	Yes	ND (consider in haematological malignancies depending and concomitant therapy)	Possible (consider if concomitant corticosteroid therapy)	Yes/yes	ND, symptom-based approach in haematological malignancies	PML, HCV, enteroviral infections
	Obinutuzumab	Potentially yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	ND, probably yes/yes	ND, symptom-based approach in haematological malignancies	Enteroviral infections
	Ofatumumab	Yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	Yes/yes	ND, symptom-based approach in haematological malignancies	

Agents targeting lymphoid or myeloid cells surface antigens: CD22, CD30, CD33, CD38

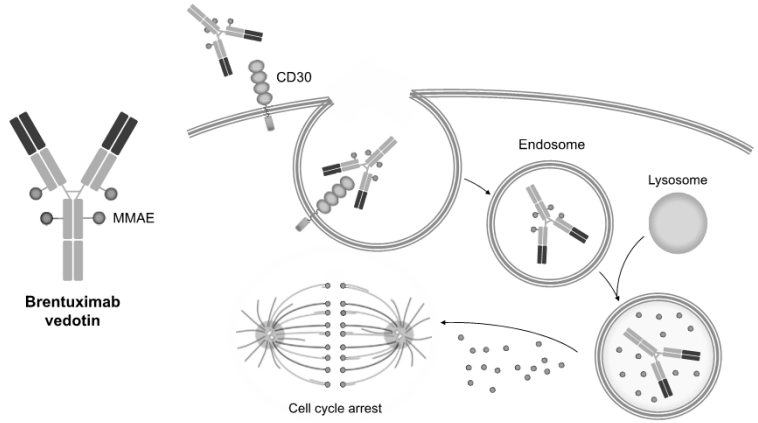
Agents targeting lymphoid or myeloid cells surface antigens



Inotuzumab ozogamicin anti-CD22
Gemtuzumb ozogamicin anti-CD33

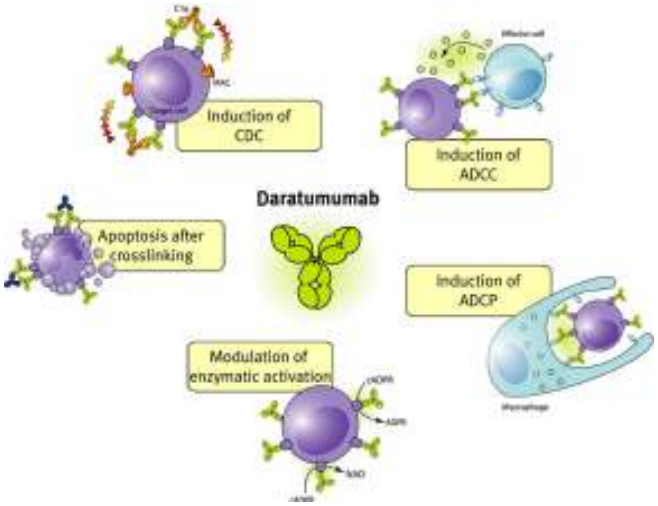
Conjugated to calicheamuiin

CD33-targeted therapy leads to profound neutropenia and thrombocytopenia



Brentuximab vedotin anti-CD30
Conjugated to Monomethyl auristatin A

may affect ADCC and exert a deleterious impact on humoral immunity



Daratumumab anti-CD38

blockade of CD38-positive immunosuppressive cells
regulatory T- (Tregs) and B-cells (Bregs) and myeloid-derived suppressor cells)
increased CD8+ T-cells effector functions.

Agents targeting lymphoid or myeloid cells surface antigens

Summary of risk of infectious complications and possible management strategies for the reviewed targeted agents

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-Pneumocystis prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for HBsAgþ/HBsAg-antiHBc+)	Risk of CMV infection (monitoring warranted)	Other
CD-22 targeted agents	Inotuzumab ozogamicin	No	No	Possible	No data (theoretically possible)	No	No data
CD-30 targeted agens	Brentuximab Vedotin	Yes	No data (most HSCT recipients received prophylaxis) **prophylaxis should be administered to autologous HSCT recipients**	No data (most HSCT recipients received prophylaxis) **prophylaxis should be administered to autologous HSCT recipients**	Yes	Yes	PML
CD33-targeted agents	Gemtuzumab ozogamicin	No	No data (patients received standard prophylaxis for AML) **prophylaxis should be administered**	No data (patients received standard prophylaxis for AML) **prophylaxis should be administered**	No data (patients received standard prophylaxis for AML) **prophylaxis should be administered**	ND (patients received standard prophylaxis for AML)	No data
CD-38 targeted	Daratumumab (no data yet available for isatuximab)	Yes	**Yes (VZV)**	**Possible (consider if concomitant corticosteroid**	**Possible (consider if concomitant corticosteroid**	No	**Seasonal influenza vaccination**

Intracellular signaling pathways: tyrosine kinase

BCR-ABL tyrosine kinase inhibitors:
imatinib, dasatinib, nilotinib, bosutinib and ponatinib

Chronic myeloid leukaemia (CML) is characterized by the (9; 22) (q34; q11) translocation

- **Imatinib:** effective against bcr-abl TK, c-kit, PDGFRα, -β
- **Dasatinib:** 300- fold more potent inhibition than imatinib, also targets the SRC family kinases, c-Kit, PDGFR-a and -b, DDR1 and ephrin receptors
- **Nilotinib:** 20 to 30 times more potent than imatinib, as well as c-Kit, PDGFR, DDR1, VEGF and ephrin receptors
- **Bosutinib:** dual-specific inhibitor of the SRC and ABL kinase families that remains active against most BCR- ABL resistance mutations, minimal activity against PDGFR and c-Kit
- **Ponatinib:** multitargeted TK inhibitor allowing BCR-ABL kinase inhibition even in presence of the T315I mutation

Expected impact on infection risk

- Myelotoxicity
- **Inhibition of CD4+ and CD8+** T-cell proliferation
- By inhibiting LCK, a member of the SRC family of TKs **imatinib and dasatinib** interfere with T-cell activation and impairs **CMV and EBV-specific CD8+ T-cell response**
- **imatinib, dasatinib or nilotinib** significantly impair B-cell responses
  - TK inhibitor-treated patients had significantly lower antipneumococcal IgM titers and lower frequencies of peripheral blood IgM memory B cells after vaccination compared to healthy controls

BCR-ABL tyrosine kinase inhibitors:
imatinib, dasatinib, nilotinib, bosutinib and ponatinib

Available clinical data

- **Imatinib** reactivation of **hepatitis B virus (HBV) infection** under imatinib treatment for CML has **been repeatedly reported**

  inhibition of the T-cell response allows intensive HBV replication

- **Dasatinib** significantly increased the risk of **CMV reactivation** during the first post- transplantation year in HSCT recipients ALL Ph+
    - sporadic reports of PCP, HBV reactivation, parvovirus B19 infection and HHV 6 reactivation

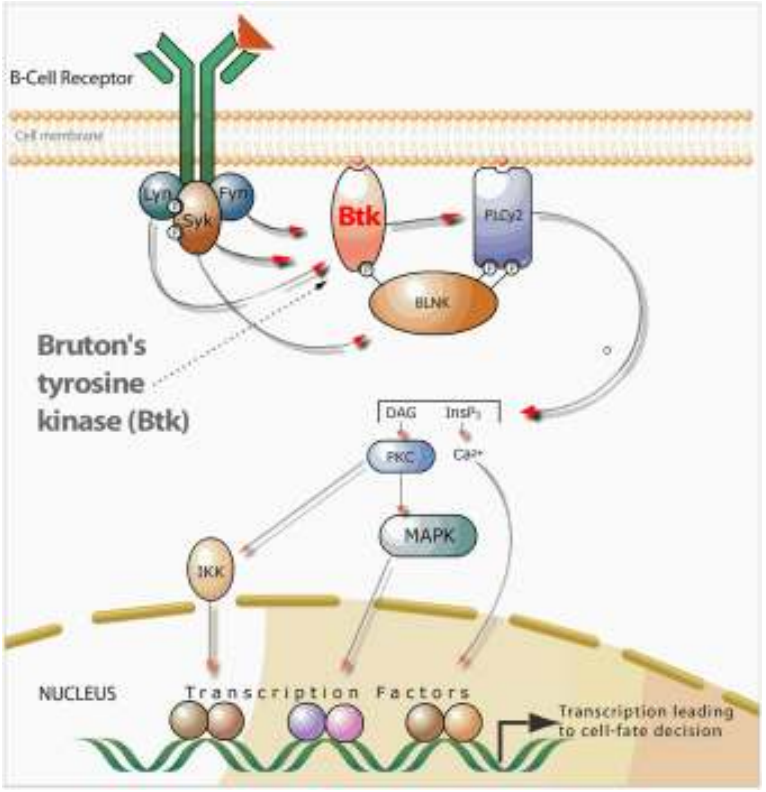
- Data on nilotinib, bosutinib, posatinib -related infection are scarce

BCR-ABL tyrosine kinase inhibitors:
imatinib, dasatinib, nilotinib, bosutinib and ponatinib

- Higher risk of **CMV infection and HBV reactivation with dasatinib** particularly (particularly after HSCT)
- **Screening for chronic HBV infection before starting therapy**
  - Antiviral prophylaxis while on therapy in HBsAg-positive patients
    Monitoring for HBV virus load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection
- No expected benefit from universal use of antibacterial, antiviral or anti-Pneumocystis prophylaxis

Bruton tyrosine kinase inhibitors: ibrutinib and acalabrutinib

- **Ibrutinib** is an inhibitor of the Bruton TK (BTK), an important signaling molecule of the BCR
  - **does not have toxic effects on normal T cells**
  - Approved for CLL, R/R Waldenstrom's Macroglobulinemia, R/R MCL
- Acalabrutinib: a second- generation, **more selective**, irreversible BTK inhibitor with improved pharmacologic features
  - FDA approved for R/R CLL, R/R MCL



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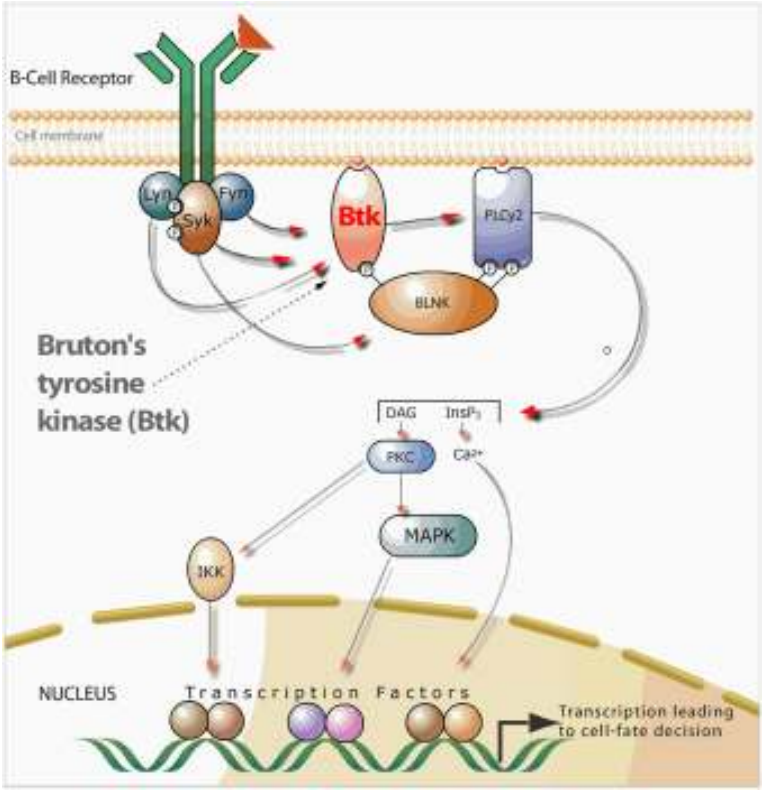
Bruton tyrosine kinase inhibitors: ibrutinib and acalabrutinib

Expected impact on infection

- Mutation of the BTK gene causes X-linked (or Bruton) agammaglobulinaemia.
  - a block in early B-cell maturation that prevents development of antibody-producing cells, with the subsequent phenotype consisting of severe, life-threatening bacterial infections

but

- increase in peripheral blood B-cell counts during the course of treatment with ibrutinib
- a more rapid immune reconstitution and
- **a significantly lower rate of infection** compared to conventional chemotherapy
- clinically meaningful recovery of humoral immune function in patients with CLL and other B-cell malignancies



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Bruton tyrosine kinase inhibitors: ibrutinib and acalabrutinib

Clinical trials data

phase 3 study comparing ibrutinib versus ofatumumab

- **Infections of any grade were also more common with ibrutinib** (70% vs. 54%), although the occurrence of episodes of grade 3 or higher was similar across both groups (24% vs. 22%).
- respiratory tract infections, **pneumonia** and urinary tract infection

- Although the expected impact on T-cell function is low, **opportunistic infections have been sporadically reported in patients treated with ibrutinib**
- **cryptococcosis, PCP, histoplasmosis, invasive aspergillosis** and disseminated fusariosis
- cases of fatal **progressive multifocal leukoencephalopathy (PML)** have been reported after the use of ibrutinib in the context of multiple prior treatment lines, including rituximab

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Bruton tyrosine kinase inhibitors: ibrutinib and acalabrutinib

Conclusions and suggested prevention strategies

- Although **no benefit is expected from the universal use of antibacterial or antifungal** prophylaxis, patients receiving ibrutinib should be **closely monitored for fever or neutropenia**, and appropriate anti-infective therapy should be instituted if appropriate.
- **Anti-Pneumocystis prophylaxis should be administered** according to current guidelines for non HIV-infected patients with haematobiologic conditions, especially in those with relapsed or **refractory CLL and additional risk factors for PCP** (i.e. alemtuzumab, purine analogue-based chemotherapy or pro- longed high-dose corticosteroids).
- **PML is a life-threatening complication** occasionally associated with the use of ibrutinib

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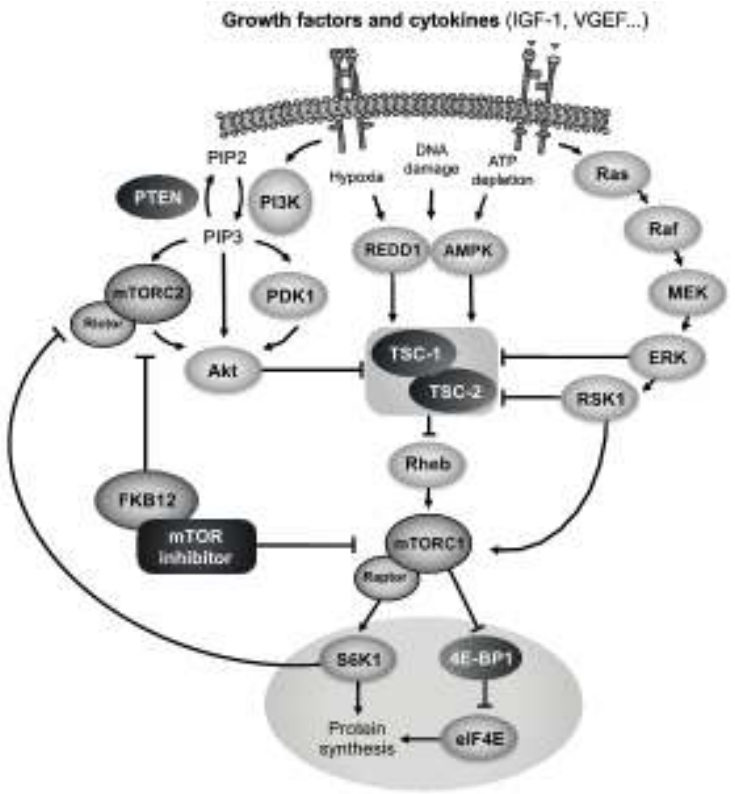
Phosphatidylinositol-3-kinase inhibitors:
idelalisib

- Idelalisib is a potent small-molecule PI3K inhibitor with highly selective activity against the d isoform
  - currently indicated in combination **with a CD20-targeted monoclonal antibody** (rituximab or ofatumumab) for **CLL** after at least one prior therapy or as first-line treatment in the presence of 17p deletion (del(17p)) or TP53 mutations in patients not eligible for alternative therapeutic approaches.
  - also indicated as monotherapy in patients with refractory **follicular lymphoma**



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Phosphatidylinositol-3-kinase inhibitors:
idelalisib, rigosertib and duvelisib

Available clinical data

Idelalisib: rash, pyrexia, diarrhoea, neutropenia, pneumonitis, hepatotoxicity and infection.

- Serious infections: PCP and CMV disease
  - Nearly all episodes of PCP, including fatal ones, occurred in the absence of specific prophylaxis.

In March 2016, the EMA analysed the results obtained from **three RCTs** of idelalisib (with or without bendamustine and rituximab) for previously untreated CLL or SLL.

- **An increased risk of death and higher incidence of serious adverse events** (including serious and/or fatal hepatotoxicity, colitis and pneumonitis)
- these results indicate that **idelalisib-related toxicity is not outweighed by the expected benefits,** in view of the favourable prognosis and low disease-related mortality of previously untreated CLL patients

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Phosphatidylinositol-3-kinase inhibitors: idelalisib, buparlisib, rigosertib and duvelisib

Conclusions and suggested prevention strategies

Anti-Pneumocystis prophylaxis is recommended for patients receiving idelalisib throughout the entire course of therapy and for **2 to 6 months after discontinuation.**

Regular monitoring for CMV infection during the course of idelalisib therapy is advisable among CMV-seropositive patients or in the presence of clinically suspected CMV disease.

Idelalisib therapy must be discontinued upon occurrence of suspected pneumonitis, grade 3/4 aminotransferase elevation (>5 times the upper reference limit) or grade 3/4 diarrhoea/ colitis.

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Antiapoptotic protein Bcl-2 inhibitors: venetoclax

- Venetoclax is a highly selective inhibitor of Bcl-2
  - approved for patients with del(17p) CLL who have received at least one prior therapy and patients with R/R CLL who have received BCRis

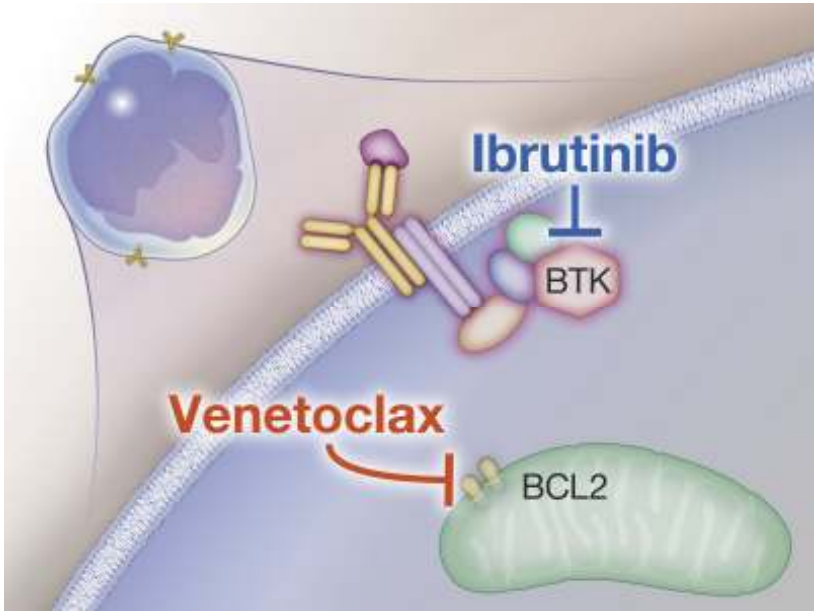
Clinical Data

Phase I **neutropenia** (considered as grade 3/4 in **41%** of participants) and **febrile neutropenia** (in about **6%**).

Phase II most common grade 3/4 adverse events were **neutropenia (40.2%)** and **infection (1.6%)**

Conclusions and suggested preventions

- In view of (limited) available data, seems **not to be associated with a meaningful increase in the risk of infection**
- **no benefit is expected from the use of antibacterial, antiviral or anti-Pneumocystis prophylaxis.**



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Janus kinase inhibitors: ruxolitinib

- Ruxolitinib targets JAK1 and JAK2 - approved MF or PV (with disease resistant to or intolerant of hydroxyurea) graft-versus-host disease

Expected impact on infection risk

- **JAK inhibitors impair T- cell function** by decreasing the potential of **producing proinflammatory cytokines**
- **Th1 and Th17 responses** result decreased both in vivo and in vitro
- severe decrease in NK cell counts, function and migration of DCs are impeded

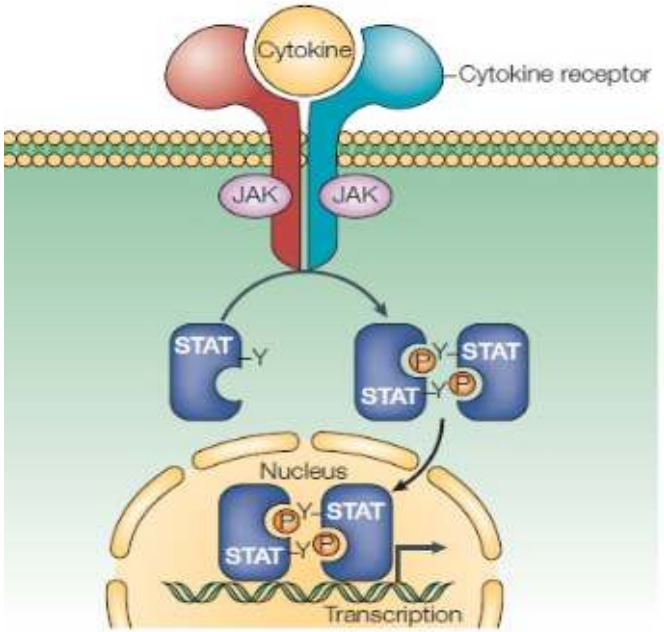
Clinical data

infection risk of infection has been repeatedly observed in clinical trials.

urinary tract infection (24.6%), pneumonia (13.1%), HZ (11.5%), sepsis and septic shock (7.9%) and tuberculosis (1.0%)

However, **grade 3/4 neutropenia** was recognized in 7.1% and 2% of patients in the ruxolitinib and placebo arms

case reports of severe opportunistic infections: such as **HBV reactivation** (including occult HBV infection reactivation in anti-HBcepositive, HBsAg-negative patients), **Cryptococcus neoformans pneumonia, PCP**, disseminated **tuberculosis** and PML.



From Nature Reviews Immunology

Blood 2013;122:4047e53.

Janus kinase inhibitors: ruxolitinib

Conclusions and suggested prevention strategies

- Screening for **chronic HBV infection** should be performed before initiating treatment with JAK inhibitors.
  - **Antiviral prophylaxis** while receiving therapy should be offered to **HBsAg-positive patients** for preventing HBV reactivation. In addition, monitoring for **HBV virus load among anti-HBc positive, HBsAg- negative** patients may be indicated to assess the eventual reactivation of occult HBV infection
- Screening for **latent tuberculosis infection may also be considered** before starting treatment with JAK inhibitors (followed by appropriate therapy if needed), as tuberculosis constitutes the most common opportunistic infection observed
- **antiviral and anti-Pneumocystis prophylaxis** in patients with additional risk factors.

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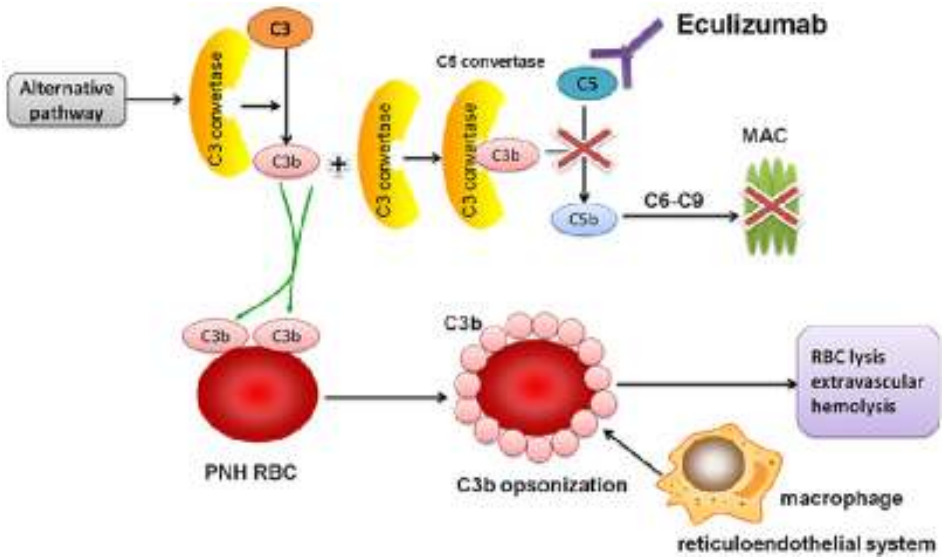
Soluble immune effector molecules: agents targeting complement factors

Complement component 5-targeted agents: eculizumab

Eculizumab (is a recombinant humanized monoclonal IgG2/4 monoclonal antibody targeting complement protein C5
Approved for PNH – aHUS-TMA



eculizumab prevents the formation of the terminal membrane attack complex (MAC) C5b-C9
MAC plays a key effector role in complement- mediated haemolysis and **extracellular killing in pyogenic infections,** especially for bacteria belonging to the genus Neisseria

Expected impact on infection

- defective bactericidal complement activity
- Nevertheless, invasive infections with encapsulated organisms like **Streptococcus pneumoniae or Haemophilus influenzae type b are rarely seen,** probably thanks to the presence of effective **upstream complement** function and opsonization
- **the risk of infection is mainly restricted to a notable increase in the susceptibility to Neisseria spp**

Complement component 5-targeted agents: eculizumab

Available clinical data

- Patients treated with eculizumab face approximately a 10 000- fold increase in the risk of meningococcal infection, with a reported incidence of up to 1.5%. In the setting of RCTs, four patients developed invasive meningococcal disease while on eculizumab, despite three of them having being previously vaccinated.
- This prompted the FDA to mandate eculizumab manufacturers to implement a Risk Evaluation and Mitigation Strategy.

Table 2
Summary of case reports of invasive meningococcal disease in patients receiving eculizumab

Reference	Age (years), gender	Underlying disorder	Vaccine type	Prophylaxis (agent)	Serogroup	Presentation	Infection onset after initiation of ECU or vaccination	Outcome
Vicente et al. 2012 [244]	27, M	PNH	Men-4ps	No	X	Septic shock	NA	Death
Rey-Mugica et al. 2013 [246]	18, M	PNH	Men-4ps	Yes, secondary	B	Sepsis	NA	Recovery
Strujik et al. 2013 [245]	19, F	aHUS, KT	Men-4ps	No	W135	Septic shock	18 months	Recovery
Applegate et al. 2016 [247]	41, M	PNH	Men-4ps	No	NA	Meningitis, septic shock	3 years	Recovery
Hernando- Real et al. 2017 [248]	23, M	PNH	MenACWY, MenB	Yes, secondary (penicillin V)	B[a]	Septic shock	4 years after initiation of ECU, 10 months after MenB	Recovery
Friedl et al. 2017 [249]	22, M	SLE-TMA	MenB, MenC	Yes, primary/secondary (ciprofloxacin)	W135	WFS, septic shock	11 months after initiation of ECU, 3 months after MenB/C, 1 month after discontinuation of prophylaxis	Recovery

Eculuzimab
Recommendations and management strategies

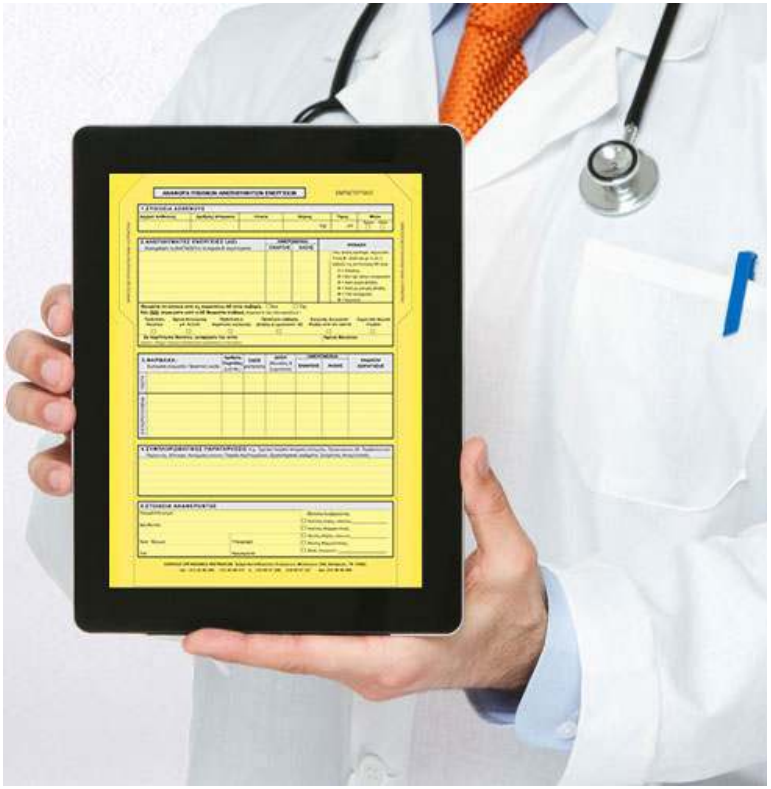
Summary of infection risks and suggested recommendations and management strategies

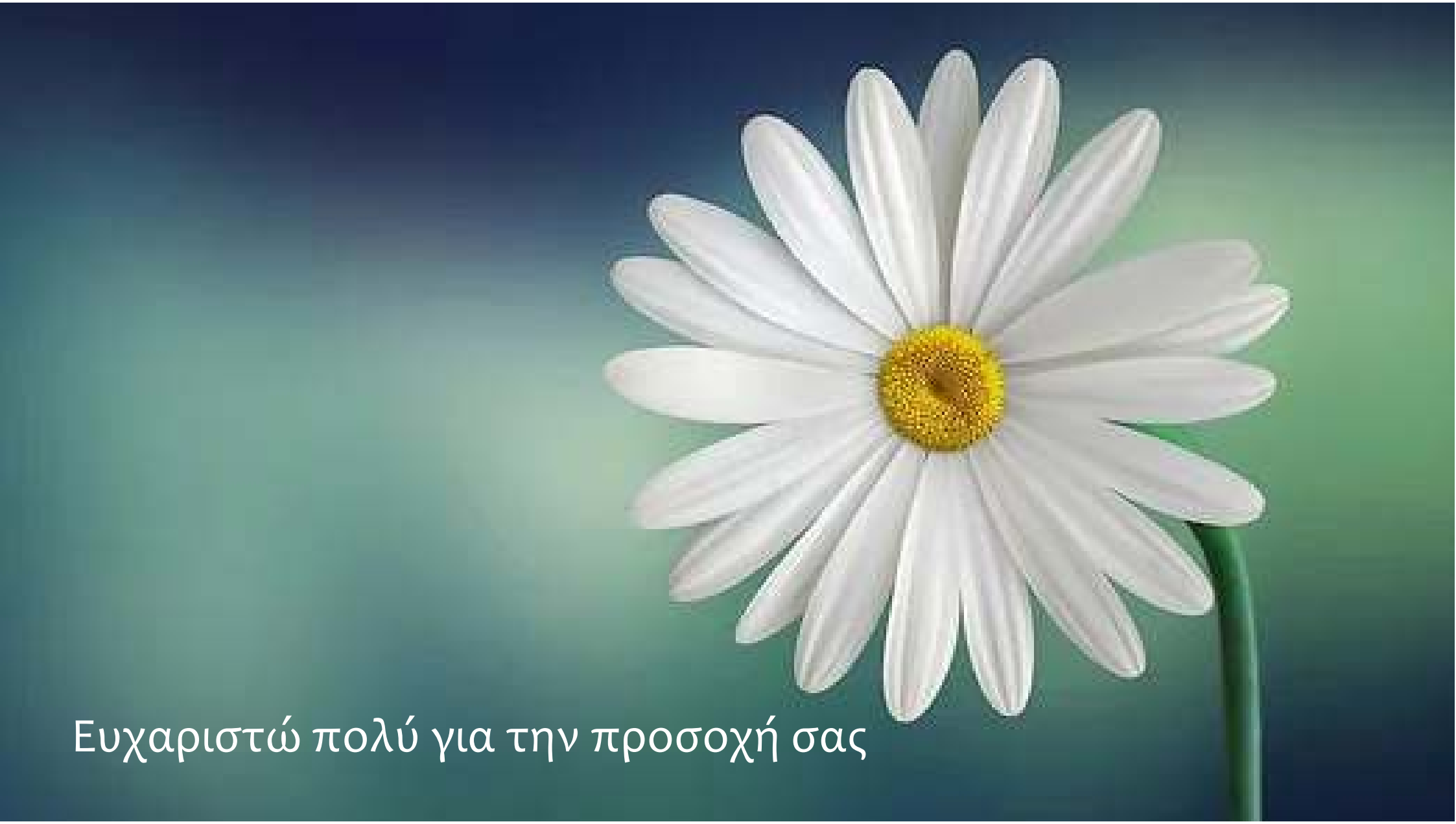
Agents	Increased risk of overall infection	Risk of VZV/HBV infection	Risk of active TB	Observations and recommendations
Eculizumab	Major (only for neisserial infections)	No /no	No	• Markedly increased risk of infection due to *Neisseria* spp. • Meningococcal vaccination (MenACWY and MenB) at least 2 –4 weeks before starting eculizumab, with booster doses of MenACWY every 5 years if therapy is maintained • Meningococcal chemoprophylaxis (penicillin V or ciprofloxacin) at least 4 weeks since completion of vaccination or until protective antibody titres are documented • Continuation of chemoprophylaxis for immunocompromised patients, with discontinuation after 4 weeks from the last dose of eculizumab • Monitoring of serum bactericidal antibody may help to guide the requirements for vaccine booster and prolongation of chemoprophylaxis • Screening for gonococcal infection in patients at high-risk for STD and their sexual partners • Pneumococcal and Hib vaccination before starting eculizumab

HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; IL, interleukin; Ig, immunoglobulin; LTBI, latent tuberculosis infection; MenACWY, meningococcal (serogroups A, C, W-135 and Y) conjugate vaccine; MenB, meningococcal serogroup B vaccine; STD, sexually transmitted disease; TB, tuberculosis; TNF-α, tumor necrosis factor-α; VZV, varicella zoster virus.

Conclusions

- **New targets - new drugs - new adverse effects – new risks**
- Hematologists need to be aware and alerted
- Collaboration with Infectious Disease doctors a necessity but wishful thinking for some of us
- **Prevention** always better than treatment
- Share your experience: Case reports and Yellow card




Ευχαριστώ πολύ για την προσοχή σας