

Bispecific monoclonal antibodies for the treatment of relapsed/refractory multiple myeloma: expert recommendations for their administration in Spanish centers

Anticuerpos biespecíficos para el tratamiento del mieloma múltiple en recaída/refractario: recomendaciones de expertos para la administración en los centros españoles

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Abstract

Bispecific antibodies (BsAbs) have emerged as a novel therapeutic option for optimizing the treatment of patients with relapsed/refractory multiple myeloma (MM), due to their efficacy in this subset of patients, which suggests an increase in their use in the upcoming years. Their safety profile requires appropriate training for their clinical use. This expert consensus outlines the minimum requirements that should be considered for the safe integration of BsAbs into the therapeutic arsenal of Spanish hospitals. The presence of an intensive care unit, the availability of tocilizumab, and adequate training of on-site healthcare professionals are essential requirements for the administration of BsAbs. Furthermore, the establishment of rapid-response healthcare circuits for patients receiving BsAbs could help prevent serious adverse events, optimizing patient management. In healthcare centers lacking these requirements, it would be advisable to establish agreements and protocols for referring patients to specialized hospitals for the safe administration of initial doses (step-up phase), while long-term follow-up may be conducted at any center equipped to manage MM patients. The use of prophylactic measures is crucial to prevent/significantly reduce the incidence of adverse events. In the future, the incorporation of preventive strategies and a deeper understanding of BsAb-associated toxicities may facilitate their out-patient administration.

Keywords: Multiple myeloma. Bispecific antibodies. Minimum requirements. Recommendations for their administration. Healthcare circuits.

Resumen

Los anticuerpos biespecíficos (AcBs) surgen como una nueva opción de tratamiento en pacientes con mieloma múltiple en recaída/refractario (MMRR) debido a la alta eficacia demostrada en esta población, previéndose un incremento en su uso en los próximos años. Su perfil de seguridad requiere de una formación adecuada. Este consenso de expertos describe los

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requisitos mínimos necesarios para la introducción segura de los AcBs en los hospitales españoles. La presencia de unidad de cuidados intensivos, la disponibilidad de tocilizumab y profesional sanitario presencial adecuadamente formado, son requisitos indispensables para la administración de AcBs. Además, establecer circuitos para asistir rápidamente a los pacientes tratados con AcBs, permitiría prevenir eventos adversos graves y optimizar su uso. Los centros que no cuentan con estos requisitos mínimos podrían establecer acuerdos con hospitales de referencia para derivar a los pacientes durante la administración de la fase de escalada del AcBs, mientras que el seguimiento a largo plazo puede realizarse en cualquier centro con capacidad para tratar a pacientes con mieloma múltiple. El uso de medidas profilácticas reduce significativamente la incidencia de eventos adversos. En el futuro, la incorporación de medidas preventivas y un mayor conocimiento en el manejo de los AcBs, podría facilitar su administración ambulatoria.

Palabras clave: Mieloma múltiple. Anticuerpos biespecíficos. Requisitos mínimos. Recomendaciones administración. Circuitos asistenciales.

Introduction

Multiple myeloma (MM) is the second most common hematological neoplasm after lymphomas, accounting for 10% of all blood malignancies¹. Its prevalence is expected to increase over the next 18 years¹, with an estimated 3,731 new cases in Spain by 2025².

Treatment options for MM have led to improvements in the overall survival (OS) of patients^{3,4}. From 3 years of OS with conventional chemotherapy, hematopoietic stem cell autologous transplant, and effective drug combinations (doublets, triplets, and quadruplets combining proteasome inhibitors [PIs], immunomodulatory drugs [IMiDs], and anti-CD38 monoclonal antibodies [MoAbs])⁴, have increased patient's survival up to 8-10 years¹.

However, most patients eventually develop MM recurrences and become refractory to standard anti-MM agents, accumulating successive lines of therapy^{5,6}. To overcome treatment resistance, novel agents with innovative mechanisms of action have been developed, with treatments based on the redirection of T lymphocytes to act directly against tumor cells (e.g., bispecific antibodies [BsAb] and T cells with chimeric antigen receptors [CAR-T])⁷. These therapeutic approaches (BsAbs and CAR-T therapy), both authorized in Spain, have some differences in terms of management. CAR-T therapies, despite the advantage of being a 1-time treatment option without the need for continuous maintenance therapy⁸, require patient planning and manufacturing (logistic barriers) and can only be administered in specialized centers, while BsAbs are 'of the shelf' treatments that can be immediately used in most types of healthcare centers treating MM patients^{6,9,10}.

Currently, there are four BsAbs authorized and three available in Spain for the treatment of patients with relapsed/refractory multiple myeloma (RRMM), who have received at least three prior therapies (including

PI, IMiD, and anti-CD38 MoAbs) and have demonstrated disease progression on the last therapy¹¹⁻¹³: elranatamab, teclistamab, and talquetamab, as well as linvoseltamab, which is unavailable yet. These agents simultaneously bind to a tumor antigen expressed on myeloma cells (B-cell maturation antigen [BCMA] for elranatamab and teclistamab; or G-protein-coupled receptor class C group 5 member D [GPRC5D] for talquetamab) and to CD3 on the T cells¹. With this double bind, BsAbs allow the redirection of patient's T lymphocytes to the myeloma cells, with subsequent T cell activation, leading to a specific immunological response against the myeloma cells¹.

In heavily pretreated RRMM patients, BsAbs have demonstrated deep and sustained responses¹⁴, with high overall response rates (61.0% elranatamab¹⁵, 63%, teclistamab¹⁶, and 74% talquetamab¹⁷) and prolonged median progression-free survival^{1,18} (17.2 [95% confidence interval (CI), 9.8-not estimable] months, elranatamab¹⁹; 11.3 [95% CI, 8.8-17.1] months, teclistamab¹⁶, and 11.2 [95% CI, 8.4-16.9] months, talquetamab¹⁷).

Encouraged by the efficacy of BsAbs as monotherapy in patients with late relapses, there are trials evaluating these agents, both as monotherapy and in combinations with other anti-myeloma drugs^{1,14,18,20}, in earlier relapses and in newly diagnosed MM as well¹⁴, aiming to optimize treatment from the early stages of MM.

BsAbs present a novel and manageable safety profile that differs from that of conventional anti-MM drugs available so far. In addition to cytopenia, a common toxicity of anti-MM drugs, two early-onset immune-mediated reactions have been described related with these new drugs^{1,14,21}: cytokine release syndrome (CRS) (incidence of 57.7% [0% grade $\geq$ 3] for elranatamab; 72% [0.6% grade $\geq$ 3] for teclistamab; and 79-75% [2-1% grade $\geq$ 3] for talquetamab once weekly [QW] and once every 2 weeks [Q2W],

respectively)^{15,17,22} and immune effector cell-associated neurotoxicity syndrome (ICANS) (3.4% for elranatamab, all grade < 3; 3% for teclistamab, all grade < 3; and 11% [2% grade ≥ 3] and 10% [4% grade ≥ 3] for talquetamab QW and Q2W, respectively)^{15,17,22}. These adverse events (AEs) are commonly associated with step-up doses, requiring close monitoring and proper management to prevent severe reactions. Moreover, there is an increased risk of infections during treatment with BsAbs²³⁻²⁵. Despite infections also being associated with other anti-MM therapies and the course of the disease, an increased severity of infections, or opportunistic infections, has been observed in patients treated with BsAbs, especially with BCMA-targeted agents^{15,26}. In contrast, GPRC5D-BsAbs have been associated with target-related events, such as oral, cutaneous, and nail toxicities^{17,27,28}.

Due to the safety profile of BsAbs, adequate and continuous training of healthcare professionals is crucial to optimize the benefits of these therapies. Several international recommendations to optimize and improve the management of these BsAb-related AEs²⁹⁻³¹ have been developed. However, due to their rapid development and approval, BsAbs have not yet been incorporated into all hospitals, and no consensus or guidelines have been established on the practical considerations necessary for their incorporation and management in clinical practice. Therefore, specific recommendations on practical aspects could help determine the minimum requirements for the use of these therapies and ensure access and equity for all patients.

This document aims to provide expert guidance and define the minimum requirements for the effective introduction of BsAbs in Spanish hospitals, as well as to issue recommendations for their administration in clinical practice as agreed upon by a group of experts in the management of BsAbs in MM, representing different regions of the country.

Materials and methods

This consensus statement was developed based on expert panel opinions, as a result of different unmet needs highlighted and discussed in a virtual advisory meeting held on March 10, 2025. First, a literature review on the use of BsAbs to treat MM was conducted using the PubMed database without any publication date or language filter. The search focused on the requirements and challenges for BsAbs administration in healthcare centers, with a focus on the Spanish environment, as well as on published recommendations

and consensus on this subject. The information gathered from the literature review was used to generate a questionnaire. The questionnaire scope entailed (1) participants' experience with BsAbs; (2) considerations for the administration of BsAbs: difficulties and infrastructure, services and specialties involved in BsAbs administration; (3) management of adverse events; and (4) training and actions needed.

The questionnaire was sent by email to the panel of experts, which comprised seven hematologists belonging to tertiary-level hospitals selected based on their experience in managing BsAbs in both research and clinical practice settings, with consideration given to the representation of different geographical areas within the country. All statements and recommendations that gathered a full consensus among the experts from the questionnaires were ratified during the meeting. Otherwise, responses without 100% consensus within the questionnaires were discussed and clarified during the expert meeting until an agreement on recommendations was reached by the panel. In accordance with previously published recommendation panels, regardless of the methodology used, consensus was considered when at least 75% of agreement between experts was reached^{32,33}.

The panel of experts was requested to develop unified criteria on requirements for BsAbs use in healthcare centers, arising from their clinical experience with triple-class refractory MM patients in the Spanish practice. All 7 authors contributed in full to discussions following the meeting and survey, to develop the recommendations in this consensus.

Results - consensus recommendations

Questionnaires were completed by all experts included in the panel before the advisory meeting. All experts have used BsAbs both in clinical trials and practice, with 28% having also used them through compassionate use or expanded access programs. Most of them (71%) have extensive experience with AcBs (> 10 patients).

Essential requirements for BsAb administration

As of the time of this consensus, the recommended dosing schedule for all available BsAbs for MM treatment includes an initial step-up dosing phase, accompanied by premedication to minimize the incidence and severity of CRS and ICANS. This is followed by a

full-dose treatment phase with variable frequency among BsAbs³⁴⁻³⁶. Likewise, all authorized BsAbs for the treatment of RRMM patients should be administered until disease progression or unacceptable toxicity³⁴⁻³⁶.

For the administration of all three available BsAbs, the considerations vary among the two relevant phases of the treatment: step-up dosing and full dosing periods.

STEP-UP DOSING PHASE

A consensus among experts was reached on the following three essential requirements for administering all BsAbs in this stage in any hospital, consistent with the published evidence (Fig. 1):

Intensive care unit (ICU)^{21,29,33,37}

The availability of an ICU in the healthcare center is necessary for administering BsAbs during the step-up dose phase, regardless of the presence of a 24-h hematologist (both on-site and off-site on-call).

ICU personnel should be trained in the management of the BsAb-related AEs, particularly CRS and ICANS.

Access to tocilizumab

The use of tocilizumab is commonly prescribed for the treatment of CRS by many experts' consensus and guidelines^{29,31,33,37}. It is widely recommended to have direct access to tocilizumab in the inpatient unit to ensure that two doses equivalent to 8 mg/kg are prepared and readily available for use if required. This would prevent delays in the administration of tocilizumab in sites where there is no on-call pharmacist available, or delays in its dispensing during the afternoon/evening.

All nurses in charge of inpatient units with control over hospitalized patients during the step-up dose period must be trained in the use of tocilizumab, ensuring its correct handling and/or administration in case of need.

In-person presence of trained healthcare professionals

The hematologist should be the main specialist responsible for the management of patients receiving BsAbs. While the presence of an on-site hematologist 24 h a day is not strictly necessary, its absence should always be covered by having an off-site on-call hematologist, in addition to adequate support from an

internal medicine specialist, or equivalent, with proper training on the management of CRS and ICANS³⁷⁻³⁹. Although the incidence of severe AEs that might require intensive care is very rare, specialists should be able to promptly identify these, so they can refer patients to the ICU if needed. Specific and in-hospital cross-functional training on CRS/ICANS management will help to prevent any worsening of initial low-grade AEs, enhancing confidence in the use of BsAbs. As well, it is essential to train the nursing staff for proper identification and monitoring of early onset AEs. The training of professionals should be practical and individualized, according to the facilities available at the center. The hematologist should be the responsible and lead the training, involving all the specialties of their hospital that they deem necessary for managing MM patients treated with BsAbs. Whenever possible, the performance of local training sessions with a multidisciplinary approach at the hospital will result in more effective, immediate, and practical training, compared with external sessions or general congresses. To support this point, it could be useful to consult reference sites, medical societies, or other stakeholders that may provide a structured training session with a multifunctional approach.

When a hospital does not have its own off-site on-call hematologist, centers can evaluate the possibility of incorporating agreements for the presence of an on-site or off-site on-call hematologist only during the step-up dose period of BsAbs administration.

FULL DOSE TREATMENT PHASE

During the full dose treatment phase of BsAb administration, the profile of AEs is, in general, better known by hematologists specialized in MM, and experts agree that it could be managed in any center treating MM patients in the outpatient unit. The most relevant AEs that hematologists should pay attention to are the infections, especially in the case of BCMA-directed BsAb, and off-tumor/on-target toxicities, in the case of BsAb directed to GPRC5D. Healthcare professionals responsible for patients undergoing BsAb treatment must be trained in the identification and management of infections, skin toxicities, weight loss, and other issues, as well as individual recommendations for managing each BsAb to ensure adequate control and resolution of issues during treatment. In addition, it is important to be aware of the medium and long-term toxicities and to be on the alert for new AEs that may appear.

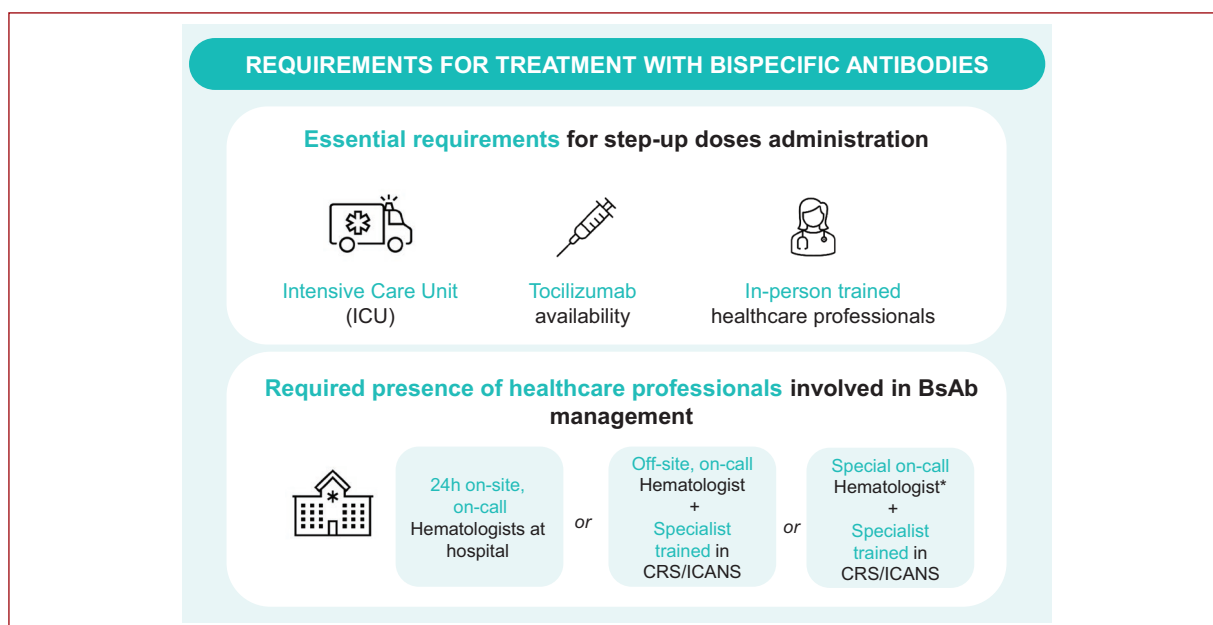


Figure 1. Requirements for the BsAb administration within the step-up dosing phase. *Special on-call Hematologist: consider formalized agreements to a) incorporate an on-call hematologist during the step-up dosing phase; or b) establish formal contract and support between the center and the referral hospital. BsAb: bispecific antibody; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit.

Healthcare circuits and specialists involved in BsAb administration

Based on the essential requirements, recommendations for the use of BsAbs should be adapted to the specific hospital characteristics. Healthcare circuits and standardized protocols should be established for access to BsAbs in all MM patients who are candidates for these novel treatments in Spain, regardless of the hospital, geographical location, or other individual local factors.

In hospitals with limited experience in the use of BsAbs in MM, it may be valuable to designate a responsible person from services directly involved in the management of patients undergoing BsAbs treatment, other than hematology, such as internal medicine, especially if there are no on-call hematologists available on-site 24 h a day. In addition to the trained healthcare professionals mentioned above, the involvement of other services will vary at each center, depending on their specific needs and available resources. In addition, when a new MM patient is admitted for initiating treatment with a BsAb, it is recommended to keep the entire team informed, including all specialists (internal medicine, neurologists, ICU personnel, among others) whose intervention might be required in case of toxicity.

Although a baseline neurological test for all patients treated with BsAbs is not mandatory (but should be recommended), in specific cases, involvement of these specialists from the beginning could be appropriate. In case of the development of any neurological AEs, the neurologist should carefully evaluate the patient.

During treatment with BsAbs, if patients need to visit the emergency department (ED), it is advisable to promptly identify these individuals on arrival and establish direct communication channels with the hematology department. Patient cards or other visual materials may be an appropriate strategy for their prompt identification. This is particularly important during the step-up dosing phase – especially when BsAbs are administered on an outpatient basis from the initial doses – as well as throughout the full dosing schedule, as it helps to reduce patient waiting times and optimize care. In addition, the involvement of infectious disease specialists may be beneficial for the early detection, management, and long-term follow-up of patients receiving BsAb therapy.

Hospitalization

Although hospitalization during treatment with BsAb is not mandatory based on the approved summary of

product characteristics (SMPc) of the available BsAbs for MM, the general recommendation from the expert panel, with special relevance in centers with little experience in its management, is to hospitalize patients during the step-up dose period, following clinical studies protocols. Specifically, SmPCs indicate 2, 3, or 4 step-up doses for elranatamab, teclistamab/talquetamab-QW, and talquetamab-Q2W, respectively.

However, it should be noted that quick bed availability may become an issue in the near future⁴⁰, especially in centers with a high volume of patients or small centers. To anticipate this issue, reference centers with a high level of expertise in the use of BsAbs might consider individual outpatient administration, requiring strategies and standardized protocols that allow rapid intervention by healthcare professionals in case of early onset AEs.

Recommendations for the management of BsAb-related toxicities

The main toxicities of BsAbs include CRS/ICANS, cytopenias, infections, and, in the case of GPRC5D-targeting BsAbs, on-target/off-tumor toxicities such as skin and nail disorders and dysgeusia³⁷.

CRS/ICANS

According to international recommendations on management of BsAb toxicities, CRS and ICANS could require mitigation strategies to decrease incidence and severity^{29,31}. In this regard, premedication is recommended before starting initial doses in the step-up schedule, as indicated in the approved prescribing information of each available BsAb³⁴⁻³⁶. Additional strategies could be required, regardless of the grade of the AE. Consequently, the availability of tocilizumab, as well as trained healthcare workers for its administration, is essential for properly managing CRS and ICANS, as described above.

CYTOPENIA AND OTHER HEMATOLOGICAL TOXICITIES

Hematological toxicities are common among anti-myeloma treatments. The management of these AEs is well-known to hematologists, without requiring additional or specific strategies in the case of BsAb administration. Dose delays and supportive care could be considered to manage hematological toxicities, following individual recommendations for each approved BsAb^{29,31,34-36}. In general, if the use of growth factors, such as granulocyte colony-stimulating factor (G-CSF),

is required, it is recommended to avoid their administration during the step-up schedule⁴¹.

INFECTIONS^{29,31,42}

Infections are commonly observed with BsAbs in MM, especially in those targeting BCMA²⁰. It is essential to have a thorough knowledge of these AEs to promptly identify infection agents and provide individualized management in each case. All experts included in the panel fully agreed on the following recommendations to prevent infections and potential severity, within the treatment with BsAbs, in concordance with previous consensus^{29,31,42}:

- Recommendations to start before the initiation of the treatment with BsAbs;
 - Evaluation of active infections and screening for hepatitis B/C and human immunodeficiency viruses.
 - Prophylaxis for viral infections with acyclovir, valacyclovir, or equivalent in all patients under treatment.
 - Prophylaxis against *Pneumocystis jirovecii* (PJP) should be provided to all patients.
 - Antibacterial and antifungal prophylaxis only in patients at high risk of infections (prolonged or chronic neutropenia despite G-CSF treatment and history of recurrent bacterial infections, fungal infections, or prolonged high-dose corticosteroid use [> 2 weeks])⁴².
 - Review and adaptation of vaccination status (vaccination against VZV recommended in RRMM patients)⁴².
 - Basal screening of cytomegalovirus (CMV), including serology and polymerase chain reaction PCR if immunoglobulin G (IgG) levels are positive.
- Recommendations to assess during the treatment with BsAbs.
 - Supplementation with exogen immunoglobulins (intravenous (IV) or subcutaneous (SC) formulations) in case of hypogammaglobulinemia, defined as IgGs levels below 400 mg/dL⁴³.
 - G-CSF, if grade 3-4 neutropenia occurs outside of the step-up dosing period⁴¹. TPO-receptor agonists in case of grade 3-4 thrombocytopenia^{44,45}.
 - Continuing with the specific prophylactic measures started before initiation.

In addition, other recommendations with no full expert consensus could be considered during treatment with BsAbs in RRMM:

- To reduce the probability of severe and opportunistic infections, consider the administration of exogen immunoglobulins (IV or SC) as primary prophylaxis,

initiated at the start of treatment with BCMA-targeting BsAbs, and continued monthly during the period when the treatment is administered weekly, regardless of immunoglobulin levels. Once the dosing schedule is reduced in frequency, and in the absence of severe infections, the prophylactic immunoglobulin administration may also be spaced out accordingly.

- CMV monitoring during treatment: routine screening for CMV reactivation is currently not universally recommended during BsAb therapy, and expert practices vary. Baseline serologic testing (CMV IgG) and quantification of CMV viral load before initiating BsAb treatment may be useful for subsequent monitoring, particularly if clinical symptoms arise during therapy. In the presence of suggestive symptoms, prompt CMV testing is strongly advised. If symptomatic CMV infection is confirmed, management should follow local institutional protocols. However, in asymptomatic patients, there are no established guidelines for managing CMV positivity detected at baseline or during treatment.
- Serology screening for additional relevant viral and bacterial infections could be considered, based on clinical judgment.
- COVID-19: due to the current status of this infection, agreement was obtained in considering COVID-19 infection as any other respiratory infection for testing and management.

Although equally necessary, some experts believe that prophylactic measures, such as primary prophylaxis with immunoglobulin supplementation, could be more lenient in the treatment with GPRC5D-targeted BsAbs.

GPRC5D-RELATED TOXICITIES

GPRC5D, in addition to being expressed in myeloma cells, is co-expressed in differentiated tissues that produce hard keratin⁴⁶, such as skin, mucous membranes, and salivary glands, causing on-target off-tumor toxicities. Therefore, skin-related AEs, dysgeusia, or weight loss are common toxicities observed in patients treated with BsAbs targeting GPRC5D^{17,20,27,47-49}. In this regard, clear recommendations for managing these AEs have not yet been established, but dose modification (mainly spacing, along with reductions, delays, or skips)⁴⁹ of the BsAb and supportive care appear to be the most effective strategies. Some of these care measures include:

- Skin hydration by use of emollients and nail hardening treatments.

- Artificial saliva, salivary stimulant, dexamethasone rinses, oral antihistamines, or other complementary medications.

- Nutritional supplements, dietary modifications, and weight monitoring.

Experts agreed that the use of emollients for hydration should be promoted as a prophylactic measure. In addition, during treatment with GPRC5D-targeted BsAbs, consultations with dermatologists and nutritionists may be necessary to optimize the management of these toxicities. In any case, experts agreed that hospitalization of patients for these AEs should only be indicated or recommended when the toxicity cannot be managed on an outpatient basis, regardless of the type or grade of the AE.

Furthermore, the development of non-ICANS neurological toxicity observed in patients treated with GPRC5D-targeted BsAbs is an important consideration for some experts. Therefore, some experts suggested that an additional recommendation for these treatments is to actively involve neurologists, regardless of the presence of hematologists and internists, for the management of these toxicities if they are reported.

Strategies to overcome the lack of minimum requirements

After assessing whether the hospital could incorporate the minimal requirements to safely administer a BsAb from the initial doses as per expert recommendations (Table 1), hospitals that cannot do so should not initiate treatment with BsAbs. The absence of resources or facilities to handle potential complications from related toxicities during the step-up dose period is the primary concern in these healthcare centers.

RECOMMENDATIONS

- Communicate with the MM experts from their reference center to evaluate the possibility of referring patients to receive the step-up dosing schedule. For this purpose:
 - Establishing local or regional referral protocols or circuits should be valuable.
 - Establishing agreements between referring and referral centers could help to create an adequate capacity and easy movement of patients for the initial doses of BsAbs.
- Experts recommend that after the step-up dose period, patients return to their original hospital to continue with the full treatment dosing (outpatient

Table 1. Checklist to confirm the capability to administer BsAbs in MM

Requirements for BsAb administration	
Essential requirements for the step-up dosing schedule	
ICU ICU personnel should be adequately trained in the management of potential severe CRS and ICANS.	Check
Tocilizumab (at least 2 doses) If doses are stored in the inpatient hospital area, nurse training must be ensured for their correct handling and/or administration.	Check
In-person trained healthcare providers who can manage any BsAb-related AEs: One of the following situations should be in place: 24-h on-site on-call hematologist at the hospital. Other specialists trained in CRS/ICANS are recommended. 24 h off-site on-call hematologist+specialists trained in CRS/ICANS. Off-site on-call hematologist during the hospitalization period* + specialists trained in CRS/ICANS (internists, intensivists...).	Check Check Check
Hospitals meeting the essential requirements	
Recommended requirements	
Establish healthcare protocols and circuits. Assess the possibility of hospitalizing the patients for the administration of step-up doses. Ensure that all specialists involved in the management of BsAb-related AEs are promptly informed when new treatments are initiated. Train all specialists in the management of initial doses and general and long-term toxicities associated with BsAbs.	
Hospitals that do not meet essential requirements for BsAb use	
Recommendations	
If the hospital is already managing MM patients, assess the possibility of incorporating the essential requirements into the hospital.	
Refer patients for the step-up dose period to a reference center: Generate referral protocols and circuits. Establish regulated agreements between referring and referral centers.	
If the hospital has an outpatient facility, with specialists in charge of MM patients, assess the possibility for the patients to continue treatment at the local center after the first full treatment dose in an outpatient setting, in the absence of incidents.	
Train specialists responsible for patients undergoing BsAb treatment in the management of frequent and long-term toxicities, such as infections.	

*Formalized agreement with a localized on-call hematologist of the referral hospital, or possibility of a localized on-call hematologist from the original center, only during the specific period of hospitalization of each patient.

AEs: adverse events; BsAbs: bispecific antibodies; CRS: cytokine release syndrome; ED: emergency department; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit; MM: multiple myeloma.

setting), with the optional possibility of staying at the reference center during the first full cycle.

- Once the patients are at their local center, training of all specialists responsible for the follow-up of the MM treatment, as well as the ED of the local center, is required on the general AE profile and how long-term toxicities observed with BsAbs should be addressed.

Concluding remarks

The new therapies emerging in the treatment of MM, such as BsAbs, require proper management to optimize their clinical benefit safely. Their introduction into the therapeutic arsenal of healthcare centers on a

country basis will allow access to innovative therapies for all patients who need them. The recommendations established in this consensus article aim to guide and support hematologists in effectively incorporating BsAbs into the therapeutic options of each healthcare center.

The expert panel that discussed the key considerations for treatment with BsAbs reached the following consensus (Fig. 2):

- It is necessary to establish monitoring measures for AEs to recognize and treat potential treatment-related toxicities early. To initiate treatment during the step-up phase, currently, it is essential to have access to an ICU, tocilizumab available on the inpatient unit, and

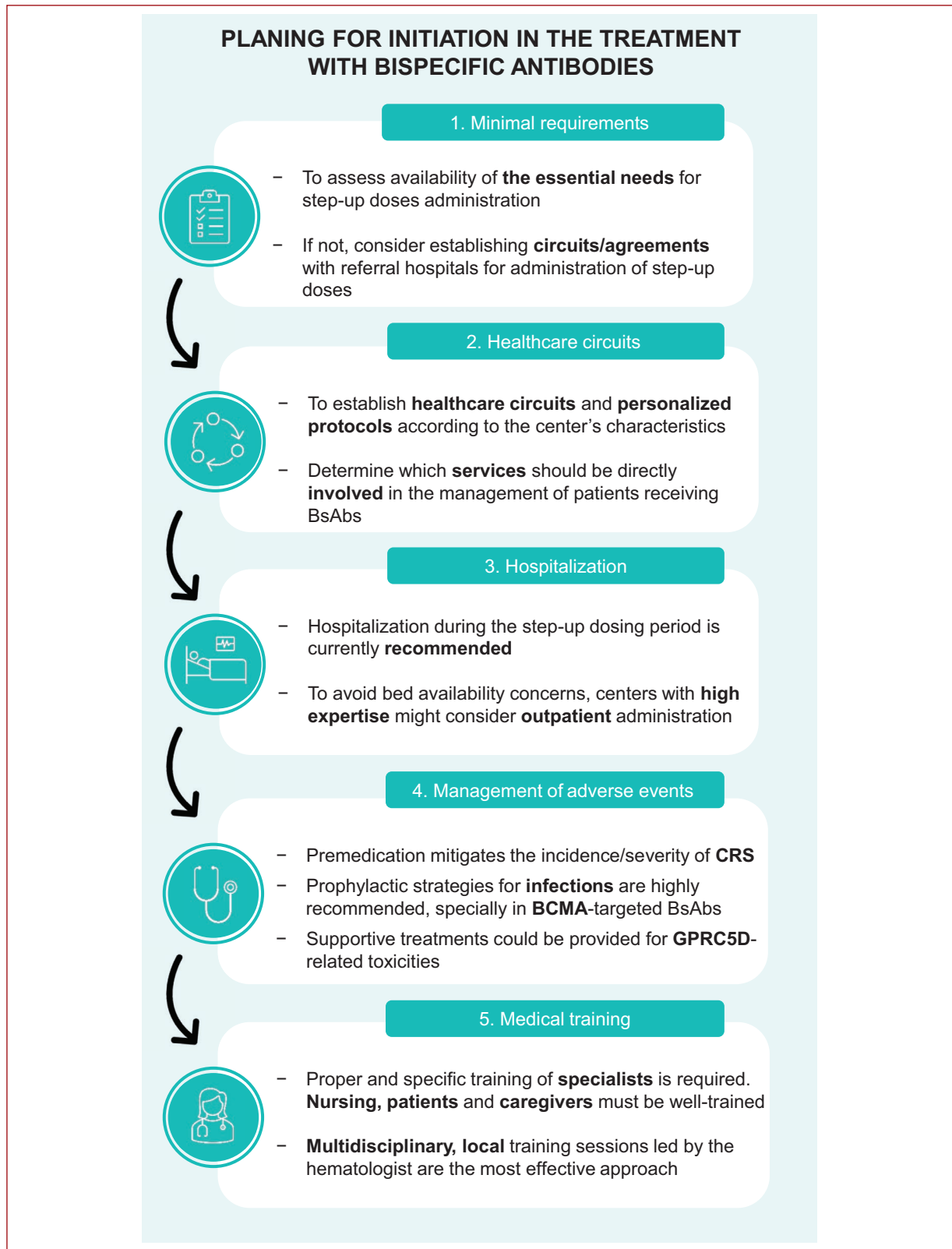


Figure 2. Consensus on the requirements and recommendations for starting the administration of bispecific antibodies. BsAb: bispecific antibody; CRS: cytokine release syndrome.

a well-trained multidisciplinary team. It is important to inform patients and their caregivers about potential toxicities to ensure early detection and treatment.

- Establishing hospital circuits is essential to ensure rapid care for patients treated with BsAbs, especially in outpatient settings, involving emergency personnel for swift referral to hematology specialists. The development of this consensus, checklists, and supportive materials could be useful for medical staff education.
- Hospitalization during the step-up dosing (SUD) period is crucial in centers lacking enough experience in initiating BsAb treatment. Outpatient administration may be considered in hospitals with high levels of training and experience in managing these therapies, particularly when there is a shortage of inpatient beds.
- The importance of using prophylactic measures to significantly reduce the occurrence of AEs is recognized, which could help less experienced centers incorporate these treatments. Among these measures, the most widely used currently is the use of immunoglobulins as infectious prophylaxis⁵⁰ and preventive strategies for CRS^{29,31}. Other strategies for skin or oral toxicities are also being tested. These include the use of tocilizumab or, more recently, dexamethasone, which may help reduce the incidence of CRS during the step-up dosing of BsAbs⁵¹.
- Centers lacking the minimum resources for step-up administration should establish referral agreements with specialized reference centers, ensuring fair access to BsAbs for all candidate patients. Local hematologists should retain responsibility for long-term follow-up, with access to expert consultation in the event of complications as needed.

Strengths and limitations

It is important to note that these recommendations are valid at the time of writing because they are based on the current context and should be viewed as flexible, as they are expected to evolve with the emergence of new data. They should be updated in the future due to the rapidly evolving therapeutic landscape of MM. As has been the case with other treatments for MM, increased familiarity, clinical use, and accumulated experience with BsAbs, together with the increasing availability of real-world clinical data, will enable a future re-evaluation of these recommendations and their adaptation to a setting with greater confidence in the management of BsAbs. Among the topics expected

to change with increasing evidence and experience with BsAb are: the duration of IgG replacement therapy due to continuous treatment, additional or different preventive strategies due to the long-term infection risk in survivors, or the actual need for ICU support given the low incidence of grade ≥ 3 AEs (such as CRS/ICANS). Regarding this last requirement, the administration of BsAb could be considered in centers without an ICU but with a well-equipped emergency room and the availability of an ICU in a referral center < 1 h away. However, the authors strongly suggest that professionals at the referring centers have gained experience and received adequate training.

Due to this changing setting, we have focused on the current requirements for starting to use BsAbs, also considering the current recommendations of international guidelines for the optimal use of BsAb and management of related toxicities³¹.

Another limitation is that the expert panel only included hematologists who belonged to tertiary-level hospitals (reference hospitals), without representative specialists of referring centers. This limitation arises from the need to have experience in managing BsAbs. Clinical trials are conducted in this healthcare setting and subsequently, the participating centers continue with the administration of the drug under investigation after obtaining its price and reimbursement. In addition, most of the hematologists involved in the expert panel maintain close relationships with those who work at the referring centers and are aware of their perspectives and needs.

Moreover, due to the full agreement reached among these Spanish experts, we envision that the requirements and recommendations presented here enable the integration of BsAbs into the practices of the current referring hospitals, ensuring access to BsAbs for all RRMM candidate patients.

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Author contributions

M.V. Mateos coordinated the project and reviewed pre-work questionnaires for the discussion. All authors

contributed to the survey results, and/or interpretation of data, and critical review of the manuscript. All authors had full access to, and contributed to the interpretation of, all data reported herein. All authors provided a final review of this manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Conflicts of interest

M.V. Mateos has received honoraria derived from lectures and participation in advisory boards for Johnson and Johnson, BMS, Amgen, Pfizer, GSK, Regeneron, Oncoceptides, Abbvie, Sanofi, Kite, Roche. J.M. Martí-Tutusa has received Honoraria derived from lectures and participation in advisory board for Johnson and Johnson, Pfizer, Menarini. A. Suárez-Cabrera has received honoraria derived from lectures and participation in advisory board for Johnson and Johnson, Amgen, Sanofi, Abbvie, Astra-Zeneca, BMS. M.J. Blanchard has received honoraria derived from lectures and participating in advisory boards for Johnson and Johnson, Pfizer, BMS, Amgen, GSK, Sanofi and Menarini. M.E. Clavero has received honoraria derived from lectures and participation in advisory board for Johnson and Johnson, Pfizer, Sanofi and BMS. M.J. Cejalvo has received honoraria derived from participation in advisory boards for Pfizer. E. Lavilla has received honoraria derived from lectures and participation for BeiOne, GSK, Incyte, Sobi, Sanofi, Abbvie, Amgen, Johnson and Johnson, Alexion, Roche, Pfizer, Novartis and BMS.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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